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PERFLUOROALKYL-CONTAINING METAL COMPLEXES AND THEIR USE IN NMR DIAGNOSTICS
[Perfluoralkylhaltige Metallkomplexe und ihre Verwendung in der NMR-Diagnostik]

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/1[1]

This invention relates to the objects characterized in the claims, that is to say, new monomeric perfluoroalkyl-substituted, paramagnetic metal complexes and complex salts, pharmaceutical agents containing these metal complexes, processes for their production and their use as contrast media in ^{1}N-NMR diagnostics and spectroscopy, x-ray diagnostics, radiodiagnostics as well as radiotherapeutic agents.

Nuclear magnetic resonance (NMR) is widely used today; it is a method of medical diagnosis that is used for in-vivo imaging by means of which one can display bodily vessels and bodily tissues (including tumors) via the measurement of the magnetic properties of the protons in the bodily water. For this purpose, for example, one uses contrast media that by influencing certain NMR parameters of the body protons (for example, relaxation times T^1 and T^2) bring about an increase in the contrast in the resulting images or make these images legible to begin with. Here, one uses, above all, complexes of paramagnetic ions such as, for example, gadolinium-containing complexes (for example, Magnevist®) on the basis of the effect of the paramagnetic ions on the shortening of the relaxation times. A measure for the shortening of the relaxation time is the relaxivity that is given in terms of $mM^{-1} \cdot sec^{-1}$.

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[1] Numbers in the margin indicate pagination in the foreign text.

Paramagnetic ions such as, for example, Gd^{3+}, Mn^{2+}, Cr^{3+}, Fe^{3+} and Cu^{2+}, cannot be administered as solutions in the free form because they are too highly toxic. To render these ions suitable for in-vivo application, they are, as a rule, complex, something that is described for the first time in EP 0 071 564 A1 (complexing with aminopolycarboxylic acids, for example, with diethylene triamine pentacetic acid [DTPA]). The di-N-methylglucamine salt of the Gd-DTPA complex is known by the name of Magnevist® and is used, among other things, for the diagnosis of tumors in the human brain and the kidney. /2

The meglumine salt of Gd-DOTA (gadolinium III complex of 1,4,7,10-tetracarboxymethyl-1,4,7,10-tetraazacyclododecane), as described in French Patent 25 39 996, is another contrast medium that proved very effective in nuclear spin tomography and that was registered under the name of Dotarem®.

But these contrast media cannot be used satisfactorily for all practical cases. The contrast media currently used for clinical purposes are distributed for modern imaging processes such as nuclear spin tomography (MRI [sic]) and computer tomography (CT) such as, for example, Magnevist®, Pro Hance®, Ultravist® and Omniscan®, are distributed in the entire extracellular space of the body (in the intravasal space and in the interstitium).

However, contrast media that during application into the vasal space (vascular space) are also exclusively distributed in

that space and that thus mark it (so-called blood pool agents) are particularly desirable for the imaging of vessels.

An attempt was made to solve these problems by using complexing agents that are bound to macromolecules or biomolecules. So far, success along these lines has been very limited.

For example, the number of paramagnetic centers in the complexes that are described in EP 0 088 695 A1 and EP 0 150 844 A1 are not sufficient for adequate imaging. If one increases the number of necessary metal ions by the multiple introduction of complexing units into a macromolecular biomolecule, then this is connected with an intolerable impairment of the affinity and/or specificity of this biomolecule [J. Nucl. Med. 24, 1158 (1983)].

Micromolecular contrast media for angiography, such as albumin-Gd-DTPA, are described in Radiology 1987; 162: 205. Albumin-Gd-DTPA, however, 24 hours after intravenous injection in rats showed an enrichment in the liver tissue that amounted to almost 30% of the dose. Besides, only 20% of the dose is eliminated over a period of 24 hours. /3

The macromolecule polylysin-Gd-DTPA (EP 0 233 619 A1) can also be used as a blood pool agent. But this compound, however, due to production factors consists of a mixture of molecules of differing size. During excretion experiments in rats, it was possible to show that this macromolecule is excreted unchanged by way of glomerular filtration via the kidney. Due to synthesis, polylysin-Gd-DTPA, however, also contains macromolecules that are

so large that during glomerular filtration, they cannot pass the capillaries of the kidney and thus remain in the body.

Macromolecular contrast media on a base of carbohydrates, for example, dextran, have also been described (EP 0 326 226 A1). The disadvantage inherent in these compounds is due to the fact that, as a rule, they carry only about 5% of the signal-reinforcing paramagnetic cation.

The object of the invention, therefore, was to provide new ^{1}H-NMR contrast media that do not present the mentioned disadvantage and that, in particular, display a higher proton relaxivity and thus permit a reduction of the dose in case of an increase in signal intensity. Furthermore, the contrast media should be stable, well tolerable and, above all, they are to display specifically organ-related properties; on the one hand, their retention in the organs to be examined should be adequate in order in case of a low dosage to get the number of images that are necessary for an unambiguous diagnosis; on the other hand, however, the fastest possible and most extensively complete excretion of the metals out of the body should be ensured subsequently.

The problem of the invention is solved with the monomeric perfluoroalkyl-containing compounds having general formula I according to Claim 1, which displays a surprisingly high proton relaxivity of 20-50 [$mM^{-1} \cdot sec^{-1}$, 39°C, 0.47 T]. In comparison to that, the proton relaxivity for the commercially available ^{1}H-

NMR contrast media Magnevist®, Dotarem®, Omniscan® and Pro Hance® shows values of between 3.5-4.9 [$mM^{-1} \cdot sec^{-1}$, 39°C, 0.47 T]. /4

In addition, the invention-based compounds are outstandingly suitable for the recognition and location of vascular diseases because, in case of application into the intravasal space, they are also exclusively distributed in that space. The invention-based compounds make it possible with the help of nuclear spin tomography to differentiate tissues with good blood circulation from tissues with poor blood circulation and thus to diagnose ischemia. Infarcted tissue can also be differentiated against surrounding healthy or ischemic tissue due to its anemia when the invention-based contrast media are used. This is particularly important when, for example, one must differentiate a heart infarct from an ischemia.

Compared to the macromolecular compounds that so far have been used as blood pool agents such as, for example, Gd-DTPA-polylysin, the invention-based compounds likewise display a higher T^1 relaxivity (see Table 3) and are thus distinguished by a great increase in the signal intensity during NMR imaging. In addition, they offer extended retention in the blood cavity; therefore, they can also be applied in relatively small dosages (amounting to, for example, $\leq$ 50 mmol Gd/kg of body weight). But, above all, the invention-based compounds that are not polymeric compounds are quickly and most extensively completely eliminated from the body.

It has furthermore been found that the compounds of the invention at hand are suitable not only as blood pool agents but can also outstandingly be employed as specifically lymph-related MRT contrast media (lymphographics).

The presentation of lymph nodes is of central significance for the early recognition of the metastatic involvement in cancer patients. The invention-based contrast media make it possible to differentiate small metastases in unenlarged lymph nodes (< 2 cm) from lymph node hyperplasias without malignant involvement.

The contrast media can be applied intravasally or interstitially/intracutaneously. Interstitial/intracutaneous application offers the advantage that the substance is transported directly from the scattering focus (for example, primary tumor) through the corresponding lymph tracts into the potentially involved regional lymph node stations. Likewise, one can achieve a high concentration of the contrast medium in the lymph nodes with a low dose. /5

The invention-based compounds meet all requirements that are expected of contrast media in indirect MRT lymphography: good local tolerability, fast elimination from the injection site, rapid and most extensively complete excretion out of the organism as a whole. Furthermore, they display a high enrichment over several lymph node stations and thus permit relevant diagnostic statements. Using the guinea pig model, it was possible to display a high degree of enrichment over several lymph node stations (popliteal, inguinal, iliacally) after s.c.

administration (2.5-10 μmol/kg of body weight, injection into the interdigital spaces of the hind paw). In particularly suitable cases, gadolinium concentrations of ≥ 200 or ≥ 300 μmol/l were obtained in the second (inguinal) and third (iliacal) stations. Lymph node concentrations in the range of 100 to 1,000 μmol/l can usually be obtained with the help of the invention-based compounds.

The particular suitability of the invention-based compounds was confirmed in the course of MR imaging studies on guinea pigs. A definite enhancement of the popliteal lymph node (270%) as well as the inguinal lymph node (104%) was observed (see Figure 1) in T^1-weighted spin echo images (TR 400 ms, TE 15 ms) just 120 minutes after subcutaneous application of 10 μmol/kg of body weight of a perfluoro-containing gadolinium complex (guinea pigs, hind paw, interdigital space).

The invention-based compounds can be injected locally in man (either subcutaneously or directly percutaneously into the tissue concerned). Several injection sites (weals) with a particular injection volume of 0.2 to 1 ml, grouped around the area of concern (for example, tumor), are possible. The total injected volume here should in no case exceed 5 ml. This means that a metal concentration of 75-100 mmol/l must be present in the formulation so that one can apply a potential clinical dose of 5-10 μmol/lg of body weight with this volume. The application site depends on whether a specific lymph drainage area from the associated tissue is to be specifically stained (for example, in

the case of gynecological or rectal tumors) or whether the unknown drainage area of a specific lesion should be displayed (ergo, the area for possible therapeutic intervention, for example, in case of melanoma or mammary carcinoma). /6

Gadolinium concentrations of at least 50 μmol/l and at most 2,500 μmol/l are needed for magnetic resonance imaging in normal lymph node tissue where the enrichment of the compound takes place. Imaging (depending on the injection site and the tissue) can be done 30 minutes or up to 4-6 hours after injection of the invention-based compounds. Using the invention-based compounds of gadolinium complexes, one can influence, above all, the T^1 relaxation times of the protons of the water of the lymph node tissue; therefore, T^1-weighted sequences are best able to document a magnetic resonance tomography enhancement of the lymph node stations. Lymph nodes very frequently are embedded in fatty tissue and the latter has a very high signal intensity in response to such sequences; therefore, fat-suppressed measurement methods are indicated. Paramagnetic gadolinium complexes in conjunction with fat-suppressed, T^1-weighted measurement sequences, compared to formulations of superparamagnetic ferric oxide particles, offer the great advantage that they permit MRT images with a higher spatial resolution with lower distortion artifacts (based on susceptibility artifacts) and with a shorter picture-taking time.

The lymph nodes are marked positively (that is to say, there is a signal rise); therefore, MRT images without contrast medium

are no longer absolutely needed for comparison purposes and the total examination time per patient can be reduced.

The new invention-based perfluoroalkyl-containing compounds having general formula I according to Claim 1 comprise both complexing agents and metal complexes. Compounds having general formula I with Z^1 as hydrogen atom are referred to complexing agents and compounds with at least one of the possible Z^1 substituents as metal ion equivalent are referred to as metal complexes. /7

The invention-based compounds having general formula I contain the following as preferred L residue:

$-CH_2-$

$-CH_2CH_2-$

$-(CH_2)_s-$ $s = 3 - 15$

$-CH_2-O-CH_2CH_2-$

$-CH_2-(O-CH_2-CH_2-)_t$ $t = 2 - 6$

$-CH_2-NH-CO-$

$-CH_2-NH-CO-CH_2-N(CH_2COOH)-SO_2-$

$-CH_2-NH-CO-CH_2-N(C_2H_5)-SO_2-$

$-CH_2-NH-CO-CH_2-N(C_{10}H_{21})-SO_2-$

$-CH_2-NH-CO-CH_2-N(C_6H_{13})-SO_2-$

$-CH_2-NH-CO-(CH_2)_{10}-N(C_2H_5)-SO_2-$

$-CH_2-NH-CO-CH_2-N(-CH_2-C_6H_5)-SO_2-$

$-CH_2-NH-CO-CH_2-N(-CH_2-CH_2-OH)SO_2-$

$-CH_2-NHCO-(CH_2)_{10}-S-CH_2CH_2-$

$-CH_2NHCOCH_2-O-CH_2CH_2-$

$-CH_2NHCO(CH_2)_{10}-O-CH_2CH_2-$

$-CH_2-C_6H_4-O-CH_2CH_2-$

$-CH_2-O-CH_2-C(CH_2-OCH_2CH_2-C_6F_{13})_2-CH_2-OCH_2-CH_2-$

$-CH_2-NHCOCH_2CH_2CON-CH_2CH_2NHCOCH_2N(C_2H_5)SO_2C_8F_{17}$

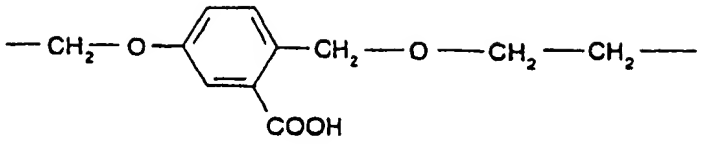
$CH_2-CH_2NHCOCH_2N(C_2H_5)-SO_2-$

$-CH_2-O-CH_2-CH(OC_{10}H_{21})-CH_2-O-CH_2CH_2-$

$-(CH_2NHCO)_4-CH_2O-CH_2CH_2-$

$-(CH_2NHCO)_3-CH_2O-CH_2CH_2-$

$-CH_2-OCH_2C(CH_2OH)_2-CH_2-O-CH_2CH_2-$

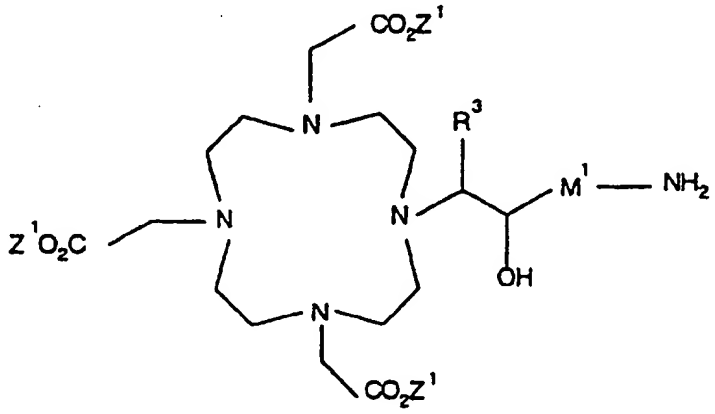


-$CH_2NHCOCH_2N(C_6H_5)$-SO_2-
-NHCO-CH_2-CH_2-
-NHCO-CH_2-O-CH_2CH_2-
-NH-CO-
-NH-CO-CH_2-$N(CH_2COOH)$-SO_2-
-NH-CO-CH_2-$N(C_2H_5)$-SO_2-
-NH-CO-CH_2-$N(C_{10}H_{21})$-SO_2-
-NH-CO-CH_2-$N(C_6H_{13})$-SO_2-
-NH-CO-$(CH_2)_{10}$-$N(C_2H_5)$-SO_2-
-NH-CO-CH_2-$N(-CH_2-C_6H_5)$-SO_2-
-NH-CO-CH_2-$N(-CH_2-CH_2-OH)SO_2$-
-NH-CO-CH_2-
-CH_2-O-C_6H_4-O-CH_2-CH_2-
-CH_2-C_6H_4-O-CH_2-CH_2-
-$N(C_2H_5)$-SO_2-
-$N(C_6H_5)$-SO_2-
-$N(C_{10}H_{21})$-SO_2-
-$N(C_6H_{13})$-SO_2-
-$N(C_2H_4OH)$-SO_2-
-$N(CH_2COOH)$-SO_2-
-$N(CH_2C_6H_5)$-SO_2-
-N-$[CH(CH_2OH)_2]$-SO_2-
-N-$[CH(CH_2OH)CH(CH_2OH)]$-SO_2-

Particularly preferred according to the invention are the L residues of the compounds mentioned in the examples given in this description of the invention.

Other preferred compounds are those in which X from formula $-C_nF_{2n}X$ signifies fluorine and where n stands for the numbers 4 to 15.

Compounds having general formula I with A having the meaning of general formula IX, where L contains at least one -NHCO- group, can be obtained from compounds having general formula 14: /9



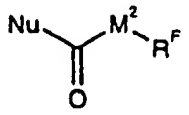
(14)

where

R^3 has the meaning given above, Z^1 has the meaning of a metal ion equivalent of the atomic numbers 21-29, 39, 42, 44 or 57-83, and

M^1 has the meaning of L,

by mixing with compounds having general formula 15:



(15)

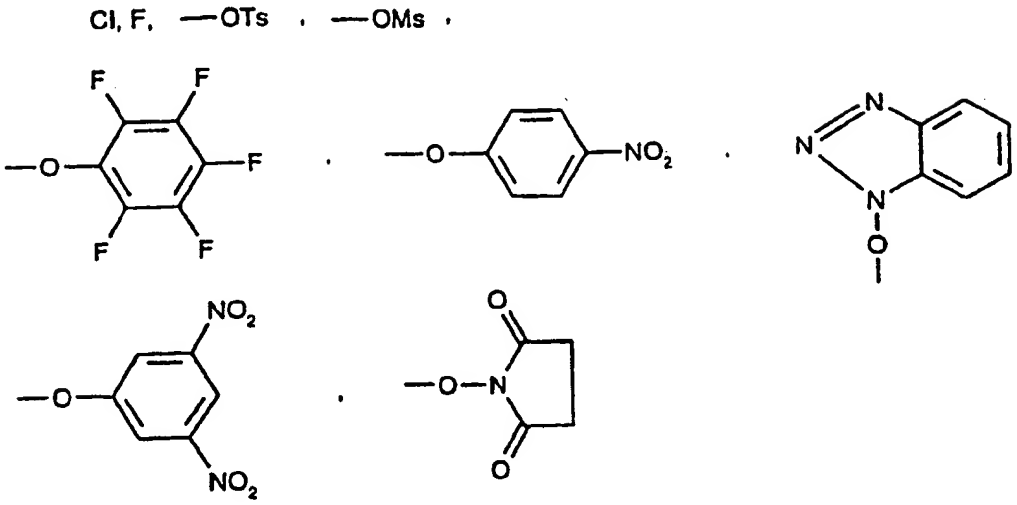
where

R^F has the above-mentioned meaning,

M^2 has the significance of L and

Nu has the meaning of a nucleofuge.

The following residues are advantageously used as nucleofuge: /10



Mixing is done in a mixture of water and organic solvents such as: isopropanol, ethanol, methanol, butanol, dioxane, tetrahydrofurane, dimethylformamide, dimethylacetamide, formamide or dichloromethane. Ternary mixtures of water, isopropanol and dichloromethane are preferred.

The mixing is done in a temperature range of between -10°C - 100°C, preferably between 0°C - 30°C.

As acid catchers, one uses inorganic and organic bases such as triethylamine, pyridine, N-methylmorpholine, diisopropylethylamine, dimethylaminopyridine, alkali and terminal alkali hydroxides, their carbonates or hydrogen carbonates as well as lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate.

Compounds having general formula 15 are obtained from compounds having general formula 16: /11

$$HO_2C\text{-}M^2\text{-}R^F \qquad (16)$$

where

R^F, M^2 have the meaning given above according to the method of acid activation generally known to the expert in the field such as by mixing the acid with dicyclohexylcarbodiimide, N-hydroxysuccinimide/dicyclohexylcarbodiimide, carbonyldiimidazole; 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, oxalic acid dichloride or chloroformic acid ester isobutylester according to the methods described in the literature on the subject:

- "Activation of Carboxylic Acids," Overview in Houben-Weyl, Methods of Organic Chemistry, Volume XV/2, Georg Thieme Publishers, Stuttgart, 19.
- "Activation with Carbodiimides," R. Schwyzer and H. Kappeler, Helv. 46: 1550 (1963).
- E. Wünsch et al., B. 100: 173 (1967).

- "Activation with Carbodiimides/Hydroxysuccinimide," J. Am. Chem. Soc. 86: 1839 (1964) as well as J. Org. Chem. 53: 3583 (1988). Synthesis 453 (1972).
- "Anhydride Method, 2-Ethoxy-1-Ethoxycarbonyl-1,2-Dihydroquinoline," B. Belleau et al., J. Am. Chem. Soc., 90: 1651 (1986), H. Kunz et al., Int. J. Pept. Prot. Res., 26: 493 (1985) and J. R. Voughn, Am. Soc. 73: 3547 (1951).
- "Imidazolide Method," B.F. Gisin, R.B. Menifield, D.C. Tosteon, Am. Soc. 91: 2691 (1969).
- "Acid Chloride Methods, Thionyl Chloride," Helv., 42: 1653 (1959).
- "Oxalyl Chlorides," J. Org. Chem., 29: 843 (1964).

Compounds having general formula 16 are commercially available (Fluorochem, ABCR) or are obtained from compounds having general formula 17:

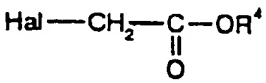
$$H\text{-}Q\text{-}M^3\text{-}R^F \quad (17)$$ /12

where

M^3 has the meaning of L and

Q has the meaning of oxygen, sulfur, a >CO group, >N-R^3, R^3-N-SO_2- with a bond from the nitrogen atom to the hydrogen atom

by mixing with compounds having general formula 18:



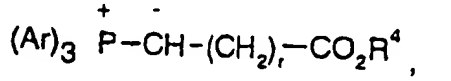
(18) /12

where

Hal has the meaning of Cl, Br, I and

R^4 has the meaning of H, methyl, ethyl, t-butyl, benzyl, isopropyl presented, for instance, according to C.F. Ward, Soc. 121, 1161 (1922), according to the methods familiar to the expert such as alkylation of alcohols with alkyl halogenides [Houben-Weyl, Methods of Organic Chemistry, Oxygen Compounds I, Part 3, Methods for the Production and Conversion of Ethers, Georg Thieme Publishers, Stuttgart, 1965; Alkylation of Alcohols with Alkyl Halogenides, p. 24; Alkylation of Alcohols with Alkyl Sulfates, p. 33] or N-alkylation of a sulfonamide with alkyl sulfonates [Houben-Weyl, Methods of Organic Chemistry, XI/2, Nitrogen Compounds, Georg Thieme Publishers, Stuttgart, 1957, p. 680; J.E. Rickman and T. Atkins, Am. Chem. Soc., 96: 2268, 1974, 96: 2268; F. Chavez and A.D. Sherry, J. Org. Chem. 1989, 54: 2990].

If Q signifies a >CO group, then the mixing is done with a Wittig reagent having the following structure: /13

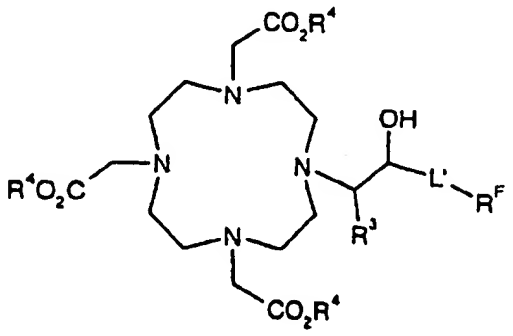


where r signifies numbers from 0 to 16.

The resultant -CH=CH double bond can be preserved as a constituent of the structure or it can be converted into a $-CH_2-CH_2$ grouping by means of catalytic hydration (Pd 5%/C).

The compounds having general formula 18 are commercially available (Fluorochem, ABCR).

As an alternative, one can obtain compounds having general formula I where A has the meaning of general formula IX from compounds general formula 19:



(19)

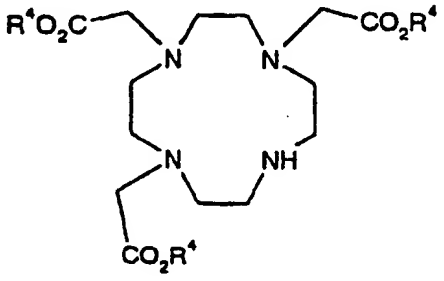
where

R^F, R^3 and R^4 have the above-mentioned meaning and

L' has the meaning of L, possibly with protective hydroxyl function or carboxyl function,

in that, if necessary, one separates existing protective groups and mixes the resultant complexing agents with the methods known to the expert (EP 250358, EP 255471) with metal oxides or metal salts at room temperature or higher temperature and subsequently, if desired, one substitutes existing acidic hydrogen atoms with cations of inorganic and/or organic bases, amino acids or amino acid amides. /14

The compounds having general formula 19 are obtained from compounds having general formula 20 (D03A or ester):

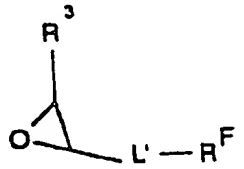


(20)

where

R^4 has the above-mentioned meaning

by mixing with compounds having general formula 21:



(21)

where

R^3 has the meaning of R^1, possibly in the protective form, or the meaning $-(CH_2)_m-L'-R^F$, where m is 0, 1 or 2 and where L' and R^F have the above-mentioned meaning. The mixing is done with alcohols such as methanol, ethanol, isopropanol, butanol, ether as well as dioxane, tetrahydrofurane, dimethoxyethers or in water or mixtures of water and one of the mentioned organic solvents as well as acetonitrile, acetone, dimethylformamide, dimethylacetamide or dimethylsulfoxide, dichloromethane, dichloroethane, chloroform at temperatures between -10°C and 180°C, preferably performed at 20° - 100°C. The addition of the following has also proved advantageous: organic or inorganic bases such as triethylamine, pyridine, dimethylaminopyridine, N-methylmorpholine, diisopropylamine, alkali- or terminal alkali hydroxides or their carbonates or hydrogen carbonates such as lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate. In the case of low-boiling epoxides, mixing is done in the autoclave. /15

Compounds having general formula 21 are commercially available (Fluorochem, ABCR) or can be obtained from compounds having general formula 22:

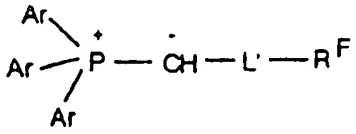
$$R^3\text{-}CH{=}CH\text{-}L'\text{-}R^F \qquad (22)$$

by epoxidizing according to methods known to the expert, for example, tungsten-catalyzed oxidation with H_2O_2 according to Payne, the cyclizing of halogen hydrines or alkaline H_2O_2 oxidation in the presence of nitriles.

Particularly suitable for this reaction is chloroperbenzoic acid in dichloromethane at room temperature. Houben-Weyl, Methods of Organic Chemistry, Oxygen Compounds I, Part 3; Methods for the Production and Conversion of Three-Member Cyclic Ethers (1,2-Epoxides), Georg Thieme Publishers, Stuttgart, 1965; G.B. Payne and P.H. Williams, J. Org. Chem., 159, 24: 54; Y. Ogata and Y. Samaki, Tetrahedron, 1964, 20: 2065; K.B. Sharpless et al., Pure Appl. Chem. 55, 589 (1983).

Compounds having general formula 22 are preferably obtained by means of Wittig reaction or by the variants according to Horner, Schlosser or Bestmann, Houben-Weyl, Methods of Organic Chemistry, XII/1, Organic Phosphorus Compounds, Part 1, Georg Thieme Publishers, Stuttgart, 1963; Phosphonium Salts, p. 79; Phosphonium Ylides, p. 112; Wittig Reaction, p. 121; A.W. Johnson, Ylides and Imines of Phosphorus, John Wiley & Sons, Inc., New York, Chichester, Brisbane, Toronto, Singapore, 1993, Wittig Reaction, p. 221; Schlosser Modification of the Wittig

Reaction, p. 240; Wadsworth-Emmons Reaction, p. 313; Horner Reaction, p. 362 by mixing a triarylphosphonium ylide.



(23) /16

with L' and R^F having the above-mentioned meaning and Ar having the meaning of aryl, in particular, phenyl with commercial methods (Merck, Fluka), or according to methods known to the expert, for example, oxidation of primary alcohols with chrome trioxide/pyridine, Houben-Weyl, Methods of Organic Chemistry, Oxygen Compounds II, Part I; Aldehydes, Georg Thieme Publishers, Stuttgart, 1954, obtainable aldehydes having general formula 20:

$$OHC\text{-}R^3 \qquad (24)$$

where

R^3 can also be H.

Triarylphosphonium ylide 23 are obtained from the corresponding halogenides having general formula 25:

$$Hal\text{-}CH_2\text{-}L'\text{-}R^F \qquad (25)$$

with Hal, L' and R^F having the above-mentioned meaning according to methods known to the expert, for example, by heating triarylphosphines with alkyl halogenide, Houben-Weyl, Methods of Organic Chemistry XII/1, Organic Phosphorus Compounds Part I, Georg Thieme Publishers, Stuttgart, 1963; or A.W. Johnson, Ylides and Imines of Phosphorus, John Wiley & Sons, Inc., New York, Chichester, Brisbane, Toronto, Singapore, 1993. The compounds having general formula 25 are commercially available (Fluorochem, ABCR, 3M).

Compounds having general formula 21 with R^3 = H are preferably obtained from compounds having general formula 17:

$$H\text{-}Q'\text{-}M^3\text{-}R^F \qquad (17)$$

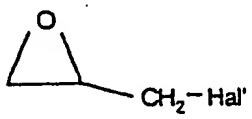
where

Q' has the meaning of Q but cannot mean any >CO group,

M^3 has the meaning of L with the exception of the direct bond and /17

R^F has the above-mentioned meaning

by mixing according to the method known to the expert involving the etherification or sulfonamide alkylation with epihalogen hydrines: (Houben-Weyl, Methods of Organic Chemistry, Oxygen Compounds I, Part 3, Methods for the Production and Conversion of Ethers, Georg Thieme Publishers, Stuttgart, 1965; Alkylation of Alcohols, pp. 24, 33; Houben-Weyl, Methods of Organic Chemistry XI/2, Nitrogen Compounds, Georg Thieme Publishers, Stuttgart, 1957, p. 680; J.E. Rickman and T.J.J. Atkins, Am. Chem. Soc. 1974, 96: 2268; F. Chavez and A.D. Sherry, 1989, 54: 2990) having general formula 26:



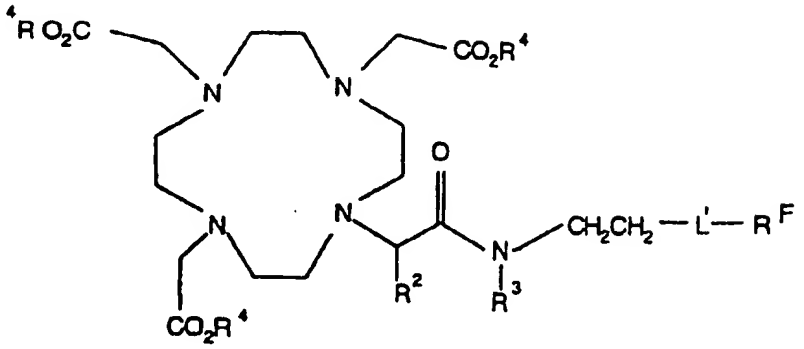
(26)

where

Hal' has the meaning of Hal, F, -OTs, OMs.

In the case of low-boiling epoxides, mixing is done in the autoclave.

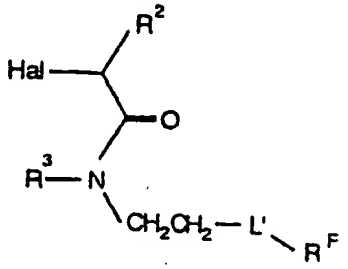
Compounds having general formula I with A having the meaning of general formula XIII can be obtained from compounds having general formula 27:



(27)

where R^2, R^3, R^4, L' and R^F has the above-mentioned meaning by separating possibly present protective groups and by complexing in the manner known to the expert. /18

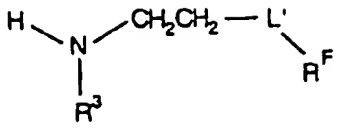
Compounds having general formula 27 can be obtained by the alkylation of compounds having general formula 20 with compounds having general formula 28:



(28)

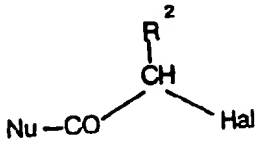
where Hal, R^2, R^3, L' and R^F have the above-mentioned meaning, in the known manner described by way of example in EP 0 232 751 B1 (Squibb).

Compounds having general formula 28 are prepared from compounds having general formula 29:



(29)

where L', R^3 and R^F have the above-mentioned meaning and an activated halogen carboxylic acid having general formula 30:



(30)

where Nu, R^2 and Hal have the above-mentioned meaning /19 according to the methods of amide formation known to the expert via activated carboxylic acids [see Bibliography, p. 11].

Compounds having general formula 30 are obtainable from acids according to C. Hell, B. 14: 891 (1881); J. Volhard, A 242, 141 (1887); N. Zelinsky, B. 20: 2026 (1887) or from the halogen acids according to the activation methods such as they were described in conjunction with general formula 15.

Compounds having general formula 29 can be obtained according to the methods known to the expert of amine synthesis [Houben-Weyl, Methods of Organic Chemistry, Nitrogen Compounds II, Amino, 1st Production, Georg Thieme Publishers, Stuttgart, 1957] from the commercial compounds (Fluorochem, ABCR) having general formula 31:

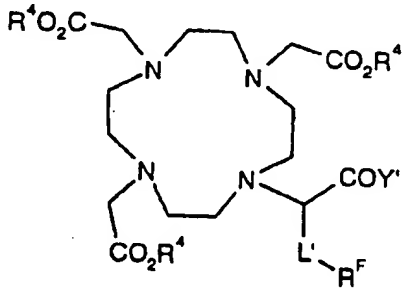
$$Hal\text{-}CH_2CH_2\text{-}L'\text{-}R^F \qquad (31)$$

or 32

$$Hal\text{-}CH_2CH_2\text{-}L'\text{-}R^F \qquad (32)$$

and they can be prepared easily, for example, by alkylation of compound 31 with an amine $PhCH_2NHR^3$ and subsequent deprotection with the amino group by means of catalytic hydration or by means of Mitsunobu reaction [H. Loibner and E. Zbiral, Helv. 59, 2100 (1976), A.K. Bose and B. Lal, Tetrahedron Lett. 3973 (1973)] of compound 32 with potassium phthalimide and deprotection with hydrazine hydrate.

Compounds having general formula I with A having the meaning of general formula VII can be obtained from compounds having general formula 33:



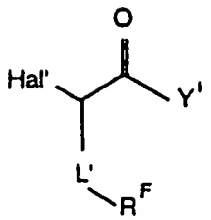
(33) /20

where

L', R^F and R^4 have the above-mentioned meaning and

Y' has the meaning of Y, possibly with protective groups by separation of possibly protective groups and complexing according to methods known to the expert (Protective Groups in Organic Synthesis, 2nd Edition, T.W. Greene and P.G.M. Wuts, John Wiley & Sons, Inc., New York, 1991; EP 0 130 934, EP 0 250 358).

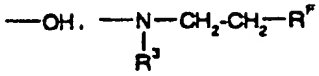
Compounds having general formula 33 can be obtained from compounds having general formula 20 and compounds having general formula 34:



(34)

where

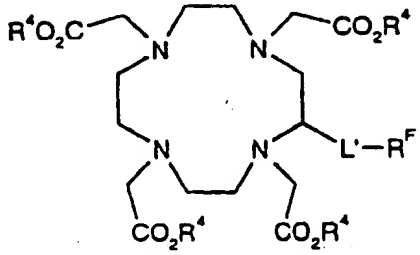
Hal', L', R^F have the above-mentioned meaning and Y' stands for the residues:



in the known manner, as described by way of example EP 0 232 751 B1, EP 0 292 689 A2 (both Squibb) or EP 0 255 471 A1 (Schering).

The preparation of compounds having general formula 34 follows known methods, for example, the Hell-Vohard-Zelinsky method consisting of commercial preliminary stages (ABCR). /21

Compounds having general formula I with A in the meaning of general formula VI can be obtained from compounds having general formula 35:

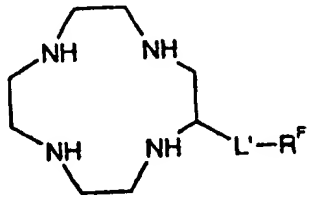


(35)

where L', R^4 and R^F have the above-mentioned meaning by possible separation from protective groups and complexing in the known manner [Protective Groups in Organic Synthesis, 2nd Edition, T.W.

Greene and P.G.M. Wuts, John Wiley & Sons, Inc., New York, 1991 (EP 0 130 934, EP 0 250 358)].

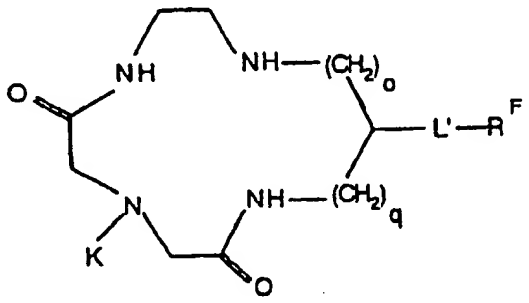
Compounds having general formula 35 can be obtained by mixing α-halogen carboxylic acid esters of acids having general formula 18 with compounds having general formula 36:



(36)

where L' and R^F have the above-mentioned meaning according to the methods known to the expert, as descried in EP 0 255 471 or U.S. Patent No. 4,885,363.

Compounds having general formula 36 can be obtained by separating any possibly present protective groups and subsequent reduction with diborane according to the known methods from compounds having general formula 37:



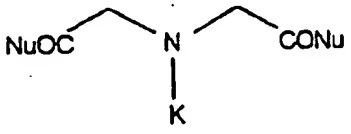
(37) /22

where

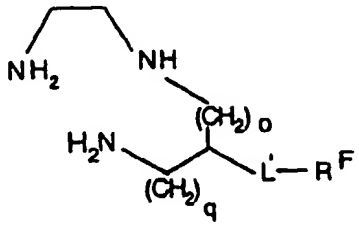
L', R^F, o, q have the above-mentioned meaning and

K has the meaning of a protective group.

Compounds having general formula 37 are accessible by means of a condensation reaction from an activated, N-protective imino diacetic acid 38 and amine 39:



(38)

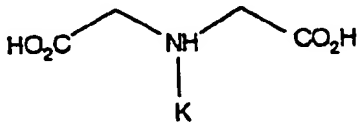


(39)

where /23

L', R^F, o, q, Nu and K have the above-mentioned meaning. As nucleofuge, one preferably uses N-hydroxysuccinimide, while as protective group, one uses the benzyloxycarbonyl-trifluoracetyl or t-butyloxycarbonyl group.

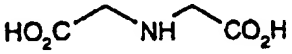
Compounds having general formula 38 can be obtained according to the method known to the expert involving the protection of the amino group and the activation of carboxylic acid [Protective Groups, Activation of Carboxyl Groups, p. 11] via the protective imino diacetic acid 40:



(40)

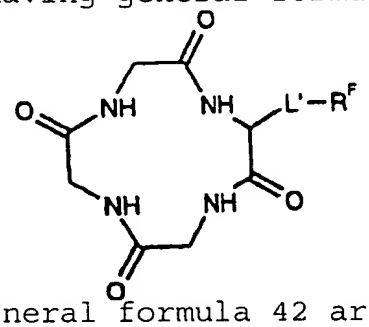
where

K has the meaning of a protective group from imino diacetic acid 41:



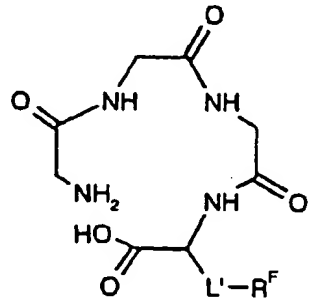
(41)

As an alternative, compounds having general formula 36 are also accessible by separation of protective groups and reduction with diborane according to the method described in conjunction with 37 from compounds having general formula 42:



(42)

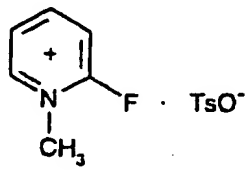
Compounds having general formula 42 are obtainable by means of ring closure of Secco compounds 43: /24



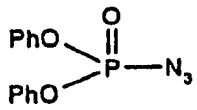
(43)

where

L' and R^F have the above-mentioned meaning according to standard methods; for instance, by mixing with the Mukaiyama reagent 2-fluoro-1-methylpyridinium-tosylate:

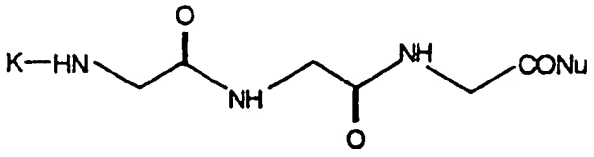


[J. Org. Chem. 1994, 59, 415; Synthetic Communications, 1995, 25, 1401] or with phosphoric acid diphenylester azide:



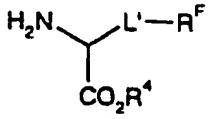
[J. Am. Chem. Soc. 1993, 115, 3420; WO 94/15925].

Compounds having general formula 43 are accessible according to the described methods by condensation of the activated acid 44:



(44) /25

where Nu and K with a compound having general formula 45:

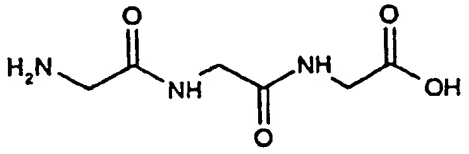


(45)

where

L', R^4 and R^F have the above-mentioned meaning.

Compounds having general formula 44 are accessible from commercial triglycine (Bachem, Fluka) 46:

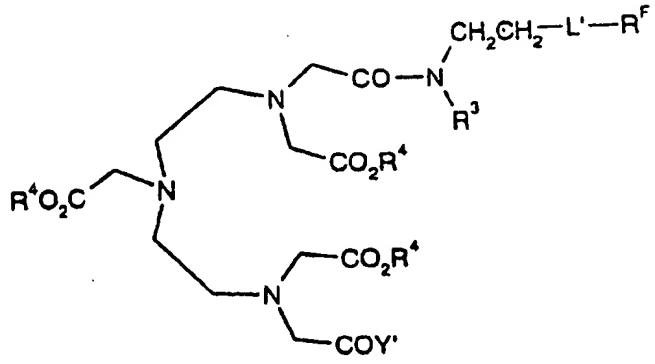


(46)

by protection of the amino group with the following activation of the acid function according to the method known to the expert for amine protection and carboxylic acid activation (Bibliography, p. 12).

Compounds having general formula 45 are easily obtainable from compounds having general formula 62 by means of the introduction of protective group R^4 according to the methods known to the expert, for example, re-esterification of a sulfite ester.

Compounds having general formula I with A having the meaning of general formula II can be obtained from compounds having general formula 47:

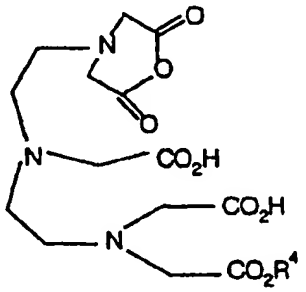


(47) /26

(47)

where L', R^3, R^4, R^F and Y' have the above-mentioned meaning, possibly by separation of protective groups and complexing in a manner well known to the expert (Protective Groups, EP 0 250 358, EP 0 130 934).

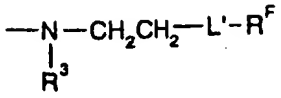
If Y' in general formula 47 signifies an OH group, then one gets the compounds by mixing compound 48:



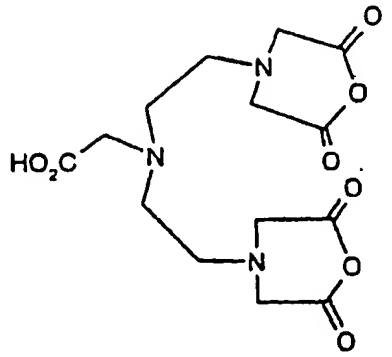
(48)

with R^4 having the above-mentioned meaning, prepared according to DE 3 633 243 with an amine having general formula 29 under previously described conditions and with subsequent separation of the protective groups.

If Y' in formula 47, however, is the group:



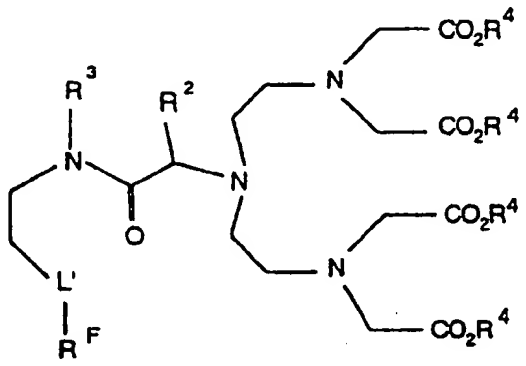
then the mixing is done with DTPA-bisanhydride (Kaufware, Merck) 49:



(49) /27

under analogous conditions.

Compounds having general formula I with A having the meaning of general formula III can be obtained from compounds having general formula 50:

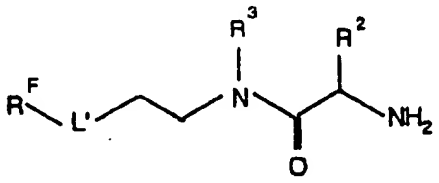


(50)

where

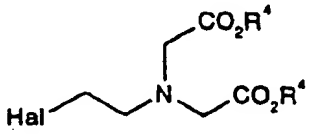
L', R^2, R^3, R^4 and R^F have the above-mentioned meaning, possibly by separation of protective groups and complexing in a manner well known to the expert (Protective Groups, EP 0 071564, EP 0 130 934, DE-OS 3 401 052].

Compounds having general formula 50 are obtained according to the method described in J. Org. Chem. 1993, 58: 1151 from compounds having general formula 51: /28



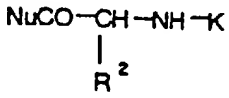
(51)

and halogen carboxylic acid derivatives having formula 52:



(52)

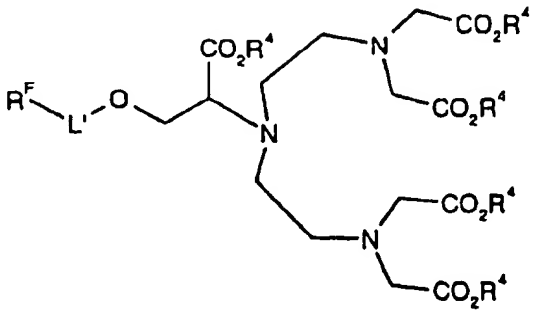
where R^4 and Hal have the previously described meaning. Compounds having general formula 51 are obtained by acylation of an amine having general formula 29 with an activated, N-protective amino acid having general formula 53:



(53)

where Nu has the above-mentioned meaning and where K has the meaning of a protective group such as Z, -BOC, FMOC, $-COCF^3$ and subsequent separation of the protective group.

Compounds having general formula I with A having the meaning of general formula IV can be obtained from compounds having general formula 54:



(54) /29

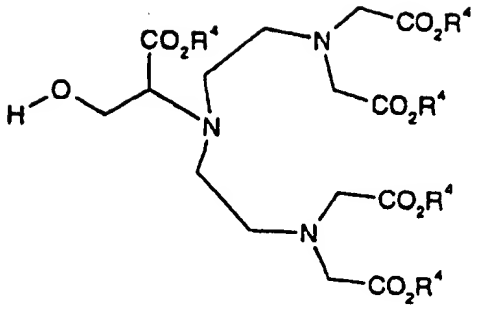
where

L', R^F and R^4 have the above-mentioned meaning, possibly by separation of protective groups and complexing in a manner well known to the expert (Protective Groups, EP 0 071 564, EP 0 130 934, DE-OS 3 401 052].

Compounds having general formula 54 can be obtained in the known manner from the halogen compounds having general formula 55:

$$Hal\text{-}L'R^F \qquad (55)$$

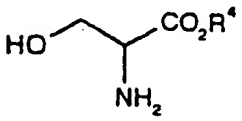
that are obtainable commercially (Fluorochem, ABCR) by mixing with hydroxy acids 56:



(56)

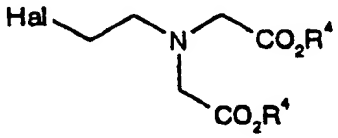
where

R^4 has the above-mentioned meaning. Compounds having general formula 56 are obtainable in the known manner according to J. Org. Chem. 58, 1151 (1993) from the commercial available Serinester 57 (Bachem, Fluka):



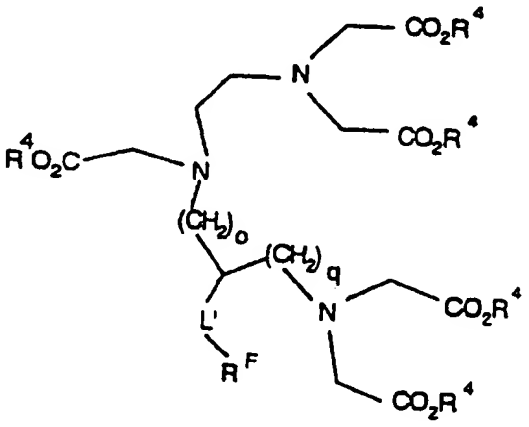
(57) /30

where R^4 has the above-mentioned meaning and the halogen carboxylic acid esters 58:



(58)

Compounds having general formula I with A having the meaning of general formula V can be obtained from compounds having general formula 59:



(59)

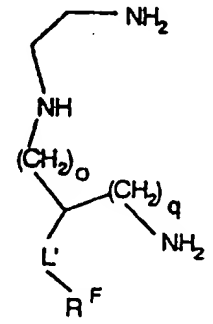
where

L', o, q, R^4 and R^F have the above-mentioned meaning, possibly by separation of protective groups and complexing in a manner well known to the expert (Protective Groups, EP 0 071 564, EP 0 130 934, DE-OS 3 401 052].

Compounds having general formula 59 can be obtained in the known manner, for example, according to J. Org. Chem., 58: 1151 (1993) by mixing of halogen carboxylic acid esters 18: /31

$$HalCH_2CO_2R^4 \qquad (18)$$

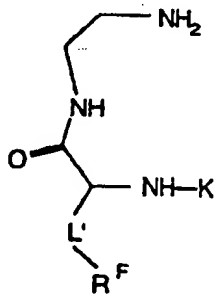
with Hal and R^4 having the above-mentioned meaning, plus a compound having general formula 39:



(39)

where L', o, q and R^F have the above-mentioned meaning.

Compounds having general formula 39, if q = 0, are obtained from compounds having general formula 60:

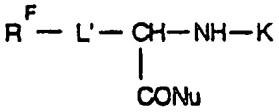


(60)

where

L', R^F and K have the above-mentioned meaning

in the known manner [Helv. Chim. Acta, 77: 23 (1994)] by reduction with diborane and separation of the protective groups. compounds having general formula 60 are obtained by aminolysis of the activated compounds having general formula 61: /32



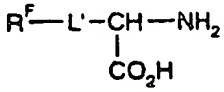
(61)

where

L', Nu, R^F and K have the above-mentioned meaning

with ethylene diamine.

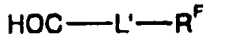
Compounds having general formula 61 are obtained according to the known methods of protective group chemistry [Protective Groups] from unprotective acid having general formula 62:



(62)

and specifically in a first step, the amino group is protected, followed by the activation of the acid group in the second step.

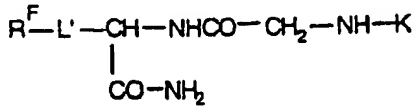
Compounds having general formula 62 can be obtained according to the methods of amino acid synthesis [Houben-Weyl, Methods of Organic Chemistry, XI/2, Nitrogen Compounds II and III, II Amino Acids; Georg Thieme Publishers, Stuttgart, 1958, Strecker Reaction, p. 305; Erlenmeyer Reaction, p. 306; Aminolysis of α-Halogen Carboxylic Acids, p. 309] from commercially obtainable aldehydes having general formula 63:



(63)

for example, according to Strecker via azlactone or via cyanohydrin.

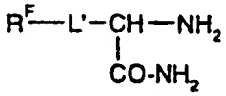
Compounds having general formula 39, if o = 0, are obtained from compounds having general formula 64: /33



(64)

where R^F, L' and K have the above-mentioned meanings in the known manner by separation of the protective groups and reduction with diborane.

Compounds having general formula 64 are accessible via aminolysis of the N-protective, activated glycines 53 with compounds having general formula 65:

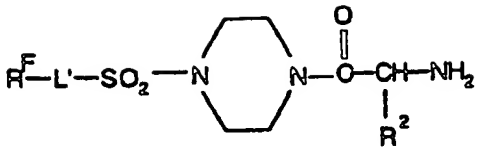


(65)

where R^F and L' have the above-mentioned meaning.

Compounds having general formula 65 are obtainable in a simple manner from compounds having general formula 61 by means of amide formation with ammonia and subsequent separation of the protective group.

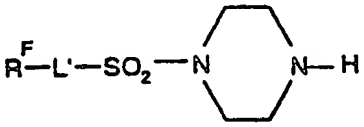
Compounds having general formula XIII can be made in analogy to compounds having general formula III in that one mixes halogen carboxylic acid derivatives having general formula 52 with compounds having general formula 66:



(66)

where R^F, L' and R^2 have the above-mentioned meaning. /34

Compounds having general formula 66 are made by mixing a compound having general formula 67:

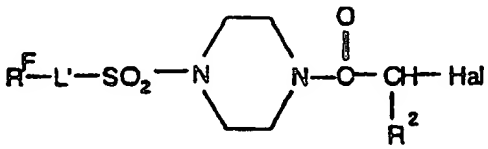


(67)

with activated, N-protective amino acid having general formula 53 in analogy to the mixing of amine 29 with compound 53.

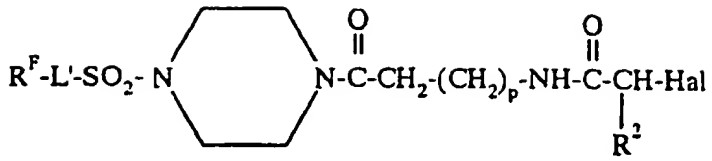
Compounds having general formula 67 may be obtained by mixing piperazine -- free or possibly partially protected -- with perfluoroalkyl sulfonic acid fluorides) or chlorides. (The formation of sulfonamide from amine and sulfofluoride is described in DOS 2 118 190, DOS 2 153 270, both Bayer AG).

Compounds having general formula XI with q having the meaning of numbers 0 or 1 are made in analogy to compounds having general formula VIII in that one mixes compounds having general formula 20 with compounds having general formula 68:



(68)

where R^F, L', R^2 and Hal have the above-mentioned meaning or with compounds having general formula 68a:



/35

(68a)

where R^F, L', R^2 and Hal have the above-mentioned meaning.

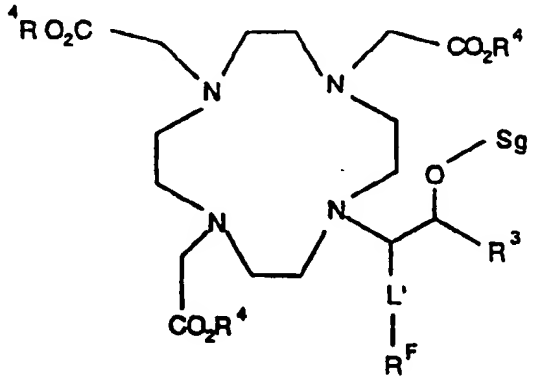
Compounds having general formula 68 can be obtained from compounds having general formula 30 and piperazine derivatives having general formula 67 in the known fashion.

Compounds having general formula 68a can be obtained from compounds having general formula 67 by means of amide coupling with compounds having general formula 68b:

(68b)

compounds having general formula XII are made in analogy to compounds having general formula II, for example, by mixing compounds having general formula 49 with piperazine derivatives having general formula 67.

Compounds having general formula I with A having the meaning of general formula X can be obtained from compounds having general formula 69:



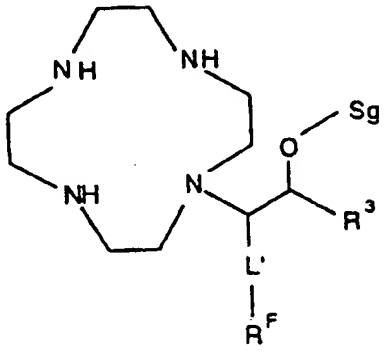
(69)

where /36

L', R^3, R^4 and R^F have the above-mentioned meaning and where Sg has the meaning of a protective group,

by possibly separating protective groups and complexing in the known fashion [Protective Groups in Organic Synthesis, 2nd Edition, T.W. Greene and P.G.M. Wuts, John Wiley & Sons, Inc., New York, 1991 (EP 0 130 934, EP 0 250 358)].

Compounds having general formula 69 can be obtained by mixing a-halogen carboxylic acid esters or a-halogen carboxylic acids having general formula 18 with compounds having general formula 70:

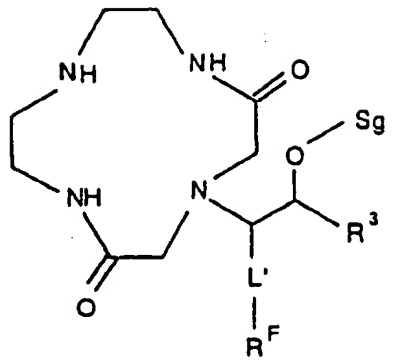


(70)

where L', R^F, R^3 and Sg have the above-mentioned meaning according to methods known to the expert, as described, by way of example, in EP 0 255 471 or U.S. Patent No. 4,885,363.

Compounds having general formula 70 are obtainable by separation of possibly present protective groups and subsequent reduction with diborane according to known methods from compounds having general formula 71:

/37

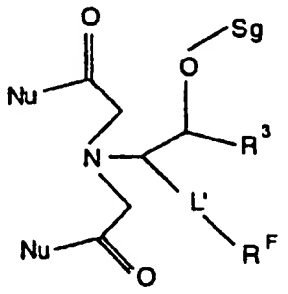


(71)

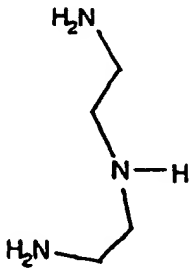
where

L', R^F, R^3 and Sg have the above-mentioned meaning.

Compounds having general formula 71 are obtainable by means of a condensation reaction from an activated iminodiacetic acid derivative having general formula 71 and diethylene triamine having formula 73:



(72)

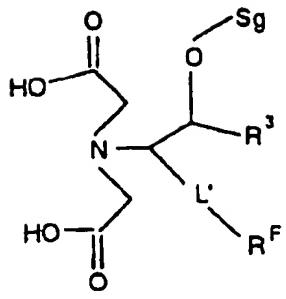


(73)

where L', R^F, R^3, Sg and Nu have the above-mentioned meaning. /38

As nucleofuge Nu, one preferably uses N-hydroxysuccinimide.

Compounds having general formula 72 can be obtained from compounds having general formula 74:



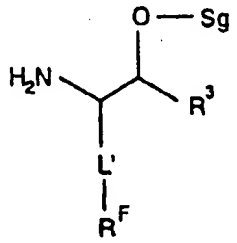
(74)

(74)

where

L', R^F and Sg have the above-mentioned meaning by activation of the carboxylic acids as described on page 11 [of original; page 13 in this document].

Compounds having general formula 74 can be obtained by mixing a-halogen carboxylic acid esters or a-halogen carboxylic acids having general formula 18 with compounds having general formula 75:

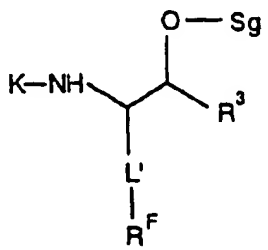


(75)

where

where L', R^F, R^3 and Sg have the above-mentioned meaning, where possibly present ester groups are saponified.

Compounds having general formula 75 can be obtained from compounds having general formula 76: /39

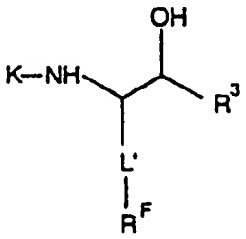


(76)

where

where L', R^F, R^3, Sg and K have the above-mentioned meaning, by separation of protective group K according to known methods.

Compounds having general formula 76 can be obtained from compounds having general formula 77:

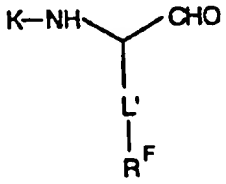


(77)

where

where L', R^F, R^3 and K have the above-mentioned meaning, by introduction of protective group Sg in the method known to the expert.

Compounds having general formula 77 can be obtained from compounds having general formula 78:



(78)

where /40

where L', R^F and K have the above-mentioned meaning, according to methods well known to the expert (Houben-Weyl, Methods of Organic Chemistry, XIII 2a, Organic Metal Compounds, Georg Thieme Publishers, Stuttgart, 1973, p. 285 ff; Mixing of Magnesium Organic Compounds with Aldehydes; p. 809 ff, Mixing of Zinc Organic Compounds with Aldehydes; Houben-Weyl, Methods of

Organic Chemistry, XIII/1, Organic Metal Compounds, Georg Thieme Publishers, Stuttgart, 1970, p. 175 ff, Mixing Lithium Organic Compounds with Aldehydes) by mixing with compounds having general formula 79:

$$Hal - R^3 \qquad (79)$$

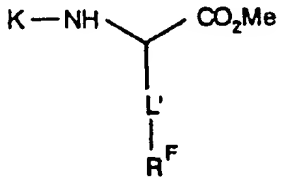
where

Hal and R^3 have the above-mentioned meaning,

obtainable in organic metal compounds such as magnesium, lithium or zinc compounds.

Compounds having general formula 79 are commercially available (ABCR, Fluka).

Compounds having general formula 78 are made from compounds having general formula 80:



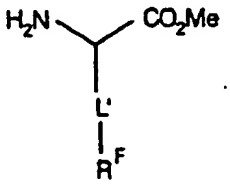
(80)

where

L', R^F and K have the above-mentioned meaning,

by reduction with diisobutylaluminum anhydride (Tett. Lett., 1962, 619; Tett. Lett., 1969, 1779; Synthesis, 1975, 617).

compounds having general formula 80 are made from compounds having general formula 45: /41



(45)

where

L' and R^F have the above-mentioned meaning

in a manner known to the expert by introducing protective group K.

Any possibly still present free carboxy groups are neutralized with the help of inorganic bases (for example, hydroxides, carbonates or bicarbonates) of, for example, sodium, potassium, lithium, magnesium or calcium and/or organic bases such as, among others, primary, secondary and tertiary amines such as, for example, ethanolamine, morpholine, glucamine, N-methyl- and N-N-dimethylglucamine as well as basic amino acids such as, for example, lysine, arginine and ornithine or of amides of originally neutral or acidic amino acids.

To make neutral complex compounds, one may, for example, add to the acidic complex salts in aqueous solution or suspension as much of the desired bases that will make it possible to reach the neutral point. The resultant solution can subsequently be concentrated in a vacuum to dryness. It is often advantageous to precipitate the formed neutral salts by adding solvents that can be mixed with water such as, for example, lower alcohols (methanol, ethanol, isopropanol and others), lower ketones (acetone and others), polar ethers (tetrahydrofurane, dioxane, 1,2-dimethoxyethane and others), thus getting crystallizates that are easy to isolate and that can be well purified. It proved to be particularly advantageous to add the desired base already during the complex formation of the reaction mixture and thus to skip one process step.

The object of the invention furthermore includes pharmaceutical agents that contain at least one physiologically tolerable compound having general formula I, possibly with the additives customary in connection with galenicals. /42

The invention-based pharmaceutical agents are produced in the known manner: One spends or dissolves the invention-based complex compounds -- possibly by adding the additives that are customary in connection with galenicals -- in an aqueous medium and one then possibly sterilizes the suspension or solution. Suitable additives are, for example, physiologically unobjectionable buffers (such as, for example, tromethamine), additives of complexing agents or weak complexes (such as, for example, diethylene triamine pentaacetic acid or the Ca complexes that correspond to the invention-based metal complexes) or -- if required -- electrolytes such as, for example, sodium chloride or -- if necessary -- antioxidants such as, for example, ascorbic acid.

If for enteral or parenteral administration or other purposes suspensions or solutions of the invention-based agents in water or in physiological salt solution are desired, then they are mixed with one or several process materials customary in conjunction with galenicals [for example, methyl-cellulose, lactose, mannite] and/or tenside(s) [for example, lecithin, Tween®, Myrj®] and/or aromatic substance(s) for purposes of taste correction [for example, etheric oils].

Basically, it is also possible to make the invention-based pharmaceutical agents without isolation of the complexes. In every case, one must be particularly careful to perform the chelate formation in such a way that the invention-based complexes will be practically free of noncomplex, toxically acting metal ions.

This can be ensured, for example, with the help of color indicators such as xylenol orange by control hydrations during the production process. The invention therefore also relates to processes for the production of complex compounds and their salts. Purification of the isolated complex is the last step to be sure as to the result. /43

The invention-based pharmaceutical agents preferably contain 0.1 μmol - 1 mol/l of the complex and, as a rule, are dosed in quantities of 0.0001-5 mMol/kg. They are intended for enteral and parenteral application. The invention-based complex compounds are used:

1. for NMR and x-ray diagnosis in the form of their complexes with the ions of the elements with the atomic numbers 21-29, 39, 42, 44 and 57-83;
2. for radiodiagnosis and radiotherapy in the form of their complexes with the radioisotopes of the elements with the atomic numbers 27, 29, 31, 32, 37-39, 43, 49, 62, 64, 70, 75 and 77.

The invention-based agents need the manifold requirements for suitability as contrast medium for nuclear spin tomography.

They are outstandingly suitable for improving the information content of the image obtained with the help of nuclear spin tomographs after oral or parenteral application due to the increase in the signal intensity. Furthermore, they display the high level of effectiveness that is necessary in order to stress the body with the smallest possible quantities of alien substances and the good tolerability that is necessary to maintain the non-invasive character of the investigations.

The good water solubility and the low osmolarity of the invention-based agents makes it possible to produce highly concentrated solutions in order thus to keep the volume load of the circulatory system within acceptable limits and to balance out the dilution by virtue of the body fluid. Furthermore, the invention-based agents offer not only a high level of in-vitro stability but also present surprising in-vivo stability so that one gets an extremely slow release or exchange of the ions that are bound in the complexes and that in themselves are toxic within the period of time during which the new contrast media are again completely excreted.

In general, the invention-based agents are dosed for use as nuclear magnetic resonance diagnostics in quantities of 0.001-5 mMol/kg, preferably 0.005-0.5 mMol/kg. Particularly low dosages (less than 1 mg/kg of body weight) of specifically organ-related NMR diagnostics can be used, for instance, to detect tumors and heart infarcts. /44

Furthermore, the invention-based complex compounds can be used advantageously as susceptibility reagents and as shift reagents for in-vivo NMR spectroscopy.

The invention-based agents are suitable also as radiodiagnostics due to their favorable radioactive properties and the good stability of the complex compounds contained in them. Details regarding this kind of use and dosage are described, for example, in "Radiotracers for Medical Applications," CRC Press, Boca Raton, Florida.

The invention-based compounds and agents can also be used in positron emission tomography, which employs positron-emitting isotopes such as, for example, ^{43}Sc, ^{44}Sc, ^{52}Fe, ^{55}Co and ^{68}Ga (Heiss, W.D.; Phelps, M.E.; Positron Emission Tomography of Brain, Springer Publishers, Berlin, Heidelberg, New York, 1983).

The invention-based compounds quite surprisingly are also suitable for the differentiation of malignant from benign tumors in regions without the blood-brain barrier.

They are also distinguished by the fact that they are completely eliminated from the body and thus are well tolerable.

The invention-based substances are enriched in malignant tumors (no diffusion into healthy tissues but a high degree of permeability of tumor vessels); therefore, they can also support radiotherapy of malignant tumors. The latter differs from the corresponding diagnosis only by the quantity and type of isotope used. The goal here is the destruction of tumor cells by means of energy-rich, shortwave radiation with the shortest possible

range. For this purpose, one uses the reciprocal effects of the metals contained in the complexes (such as, for example, iron or gadolinium) with ionizing radiation (for example, x-rays) or with neutron rays. As a result of this effect, the ray dose is significantly increased at the site where the metal complex is (for example, in tumors). To generate the same ray dose in malignant tissue, one can -- when one uses such metal complexes -- considerably reduce the radiation stress for healthy tissue and one can thus avoid any stressing side effects for the patients. The invention-based metal complex conjugates are therefore also suitable as radiosensitizing substance in connection with the radiotherapy of malignant tumors (for example, use of Mossbauer effects or in conjunction with neutron capture therapy). Suitable β-emitting ions are, for example, ^{46}Sc, ^{47}Sc, ^{48}Sc, ^{72}Ga, ^{73}Ga and ^{90}Y. Suitable α-emitting ions that have short half-life times are, for example, ^{211}Bi, ^{212}Bi, ^{213}Bi and ^{214}Bi, where ^{212}Bi is preferred. A suitable ion that emits photons and electrons is ^{158}Gd that can be obtained from ^{157}Gd by means of neutron capture. /45

If the invention-based agent is intended for use in the variant of radiotherapy proposed by R.L. Mills et al. (Nature, Vol. 336 (1998), p. 787), then the central ion must be derived from a Mossbauer isotope such as, for example, ^{57}Fe or ^{151}Eu.

In the case of the in-vivo application of the invention-based agents, they can be administered together with a suitable carrier such as, for example, serum or a physiological common

salt solution and together with another protein such as, for example, Human Serum Albumin. The dosage here depends on the type of cellular disorder, the metal ion used and the type of imaging method.

The invention-based agents are usually applied parenterally, preferably i.v. As mentioned earlier, they can also be applied intravasally or interstitially/intracutaneously, depending on whether the body vessels or the body tissues are to be investigated.

The invention-based agents are outstandingly suitable as x-ray contrast media; here it must be particularly emphasized that in working with them, one cannot detect any signs of the anaphylactic-like reactions in biochemical-pharmacological investigations that are known from the iodine-containing contrast media. They are particularly valuable due to the favorable absorption properties in areas of higher tube voltages for digital subtraction techniques. /46

In general, the invention-based agents are dosed in quantities of 0.1-5 mMol/kg, preferably 0.25-1 mMol/kg, as x-ray contrast media in analogy, for example, to meglumine diatrizoate.

On the whole, it was possible to synthesize new complexing agents, metal complexes and metal complex salts that open up new possibilities in diagnostic and therapeutic medicine.

The following examples will help present a more detailed explanation of the object of the invention:

Example 1 /47

a) N-ethyl-N-(perfluoroctylsulfonyl)-amino-acetic acid-t-butylester

20 g (37.94 mmol) of N-ethylperfluoroctyl sulfonamide and 15.73 g (113.8 mmol) of potassium carbonate are suspended in 200 ml of acetone and 14.80 g (75.87 mmol) of bromoacetic acid-tert.-butylester are dripped in at 60°C. One stirs for 3 hours at 60°C. One filters off the salts and one evaporates the filtrate in a vacuum to dryness. The residue is chromatographed in silica gel (process agent: hexane/dichloromethane/acetone = 10/10/1). After evaporation of the product-containing fractions, one crystallizes the residue from methanol/ether.

Yield: 21.66 g (89% of theoretical) of a wax-like, colorless solid.

Elementary analysis:

Calculated:	C 29.96	H 2.51	F 50.36	N 2.18	S 5.00
Found:	C 29.81	H 2.70	F 50.15	N 2.30	S 4.83

b) N-ethyl-N-(perfluoroctylsulfonyl)-amino-acetic acid

20 g (31.18 mmol) of the title compound from Example 1a) are dissolved in 200 ml of trifluoracetic acid and are stirred at room temperature overnight. One evaporates in a vacuum to dryness. The residue is recrystallized from methanol/ether.

Yield: 17.34 g (85% of theoretical) of a colorless, crystalline solid.

Elementary analysis:

Calculated:	C 24.63	H 1.38	F 55.19	N 2.39	S 5.48
Found:	C 24.48	H 1.50	F 55.01	N 2.17	S 5.49

c) Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluoroctylsulfonyl)-nonyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane.

10 g (17.09 mmol) of the title compound from Example 1b) and 1.97 g (18.79 mmol) of N-hydroxysuccinimide are dissolved in a mixture of 50 ml of dimethylformamide/50 ml of chloroform. At 0°C, one adds 3.88 g (18.79 mmol) of dicyclohexylcarbodiimide and one stirs for 1 hour at 0°C; the one stirs for 3 hours at room temperature. One again cools down to 0°C and one adds 5.19 g (51.27 mmol) of triethylamine/50 ml of 2-propanol. Then one adds 10.78 g (18.79 mmol) of gadolinium complex of 10-(3-amino-2-hydroxy-propyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (WO 95/17451) dissolved in 50 ml of water and one stirs for 3 hours at room temperature. One evaporates to dryness, one absorbs the residue in a mixture of 200 ml of methanol/100 ml of chloroform and one filters off the dicyclohexylurea. The filtrate is evaporated to dryness and is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-propanol/acetonitrile). /48

Yield: 16.37 g (78% of theoretical) of a colorless, glassy solid.

Water content: 7.1%.

T_1 relaxivity (L/mmol·sec) at 20 MHz, 37°C.

41 (water)

49 (human plasma)

Elementary analysis (related to anhydrous substance):

Calculated: C 30.58 H 3.18 F 28.31 Gd 13.78 N 7.37 S 2.81

Found: C 30.40 H 3.29 F 28.14 Gd 13.55 N 7.28 S 2.65

d) 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluoroctylsulfonyl)-nonyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

10 g (8.76 mmol) of the title compound from Example 1c) are dissolved in a mixture consisting of 100 ml of water/100 ml of ethanol and one adds 1.73 g (13.71 mmol) of oxalic acid dihydrate. One heats to 80°C for 8 hours. One cools down to 0°C and one filters off the precipitated gadolinium oxalate. The filtrate is evaporated to dryness and the residue is purified on RP-18 (RP-18/process agent: gradient from water/i-propanol/acetonitrile).

Yield: 8.96 g (94% of theoretical) of a glassy solid.

Water content: 9.3%.

Elementary analysis (related to anhydrous substance):

Calculated: C 35.30 H 3.98 F 32.73 N 8.52 S 3.25

Found: C 35.10 H 4.15 F 32.51 N 8.35 S 3.15 /49

e) Manganese complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluoroctylsulfonyl)-nonyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (as sodium salt)

5 g (5.07 mmol) of the title compound from Example 1d) are dissolved in 100 ml of water and one adds 0.58 g (5.07 mmol) of manganese (II) carbonate. One stirs for 3 hours at 80°C. The solution is filtered and the filtrate is set at a pH of 7.2 with 1N of caustic soda; this is followed by freeze drying.

Yield: 5.87 g (quantitative) of a colorless, amorphous powder.

Water content: 8.4%.

T_1 relaxivity (L/mmol·sec) at 20 MHz, 37°C:

2.7 (water)

4.2 (human plasma)

Elementary analysis (related to anhydrous substance):

Calculated: C 32.81 H 3.42 F 30.42 Mn 5.17 N 7.92 Na 2.17 S 3.02

Found: C 32.62 H 3.57 F 30.21 Mn 5.06 N 7.80 Na 2.01 S 2.90

f) Ytterbium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluoroctylsulfonyl)-nonyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

One adds 1.33 g (2.53 mmol) of ytterbium carbonate to 5 g (5.07 mmol) of the title compound from Example 1d) in 100 ml of water/30 ml of ethanol and one stirs for 3 hours at 80°C. The solution is filtered and the filtrate is evaporated to dryness in a vacuum.

Yield: 6.36 g (quantitative) of a glassy solid.

Water content: 7.8%.

Elementary analysis (related to anhydrous substance): /50

Calculated: C 30.11 H 3.14 F 27.92 N 7.27 S 2.77 Yb 14.96

Found: C 30.02 H 3.27 F 27.80 N 7.10 S 2.68 Yb 14.75

g) Dysprosium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluoroctylsulfonyl)-nonyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

One adds 0.95 g (2.53 mmol) of dysprosium oxide to 5 g (5.07 mmol) of the title compound from Example 1d) in 100 ml of water/30 ml of ethanol and one stirs for 3 hours at 80°C. The solution is filtered and the filtrate is evaporated to dryness in a vacuum.

Yield: 6.35 g (quantitative) of a colorless, glassy solid.

Water content: 8.5%.

Elementary analysis (related to anhydrous substance):

Calculated: C 30.39 H 3.17 F 28.18 N 7.33 S 2.80 Dy 14.18

Found: C 30.17 H 3.25 F 28.03 N 7.21 S 2.65 Yb 14.00

Example 2

a) 13,13,13,12,12,11,11,10,10,9,9,8,8,7,7,6,6-heptadecafluoro-3-oxa-tridecanic acid-t.-butylester

To a mixture consisting of 10 g (21.55 mmol) of 1H,1H,2H,2H-perfluorodecane-1-ol and 0.73 g (2.15 mmol) of tetrabutylammonium hydrogen sulfate in 100 ml of 60% caustic potash solution/50 ml of toluene, one drips in, while stirring forcefully at 0°C, 10.51 g (53.9 mmol) of bromoacetic acid-tert.-butylester. One stirs for 1 hour at 0°C. One adds 200 ml of toluene, the aqueous phase is separated, and one extracts twice with 50 ml of toluene each. The combined organic phases are dried over magnesium sulfate and are evaporated in a vacuum. The residue is chromatographed on silica gel (process agent: hexane/dichloromethane/acetone = 20/10/1). /51

Yield: 9.72 g (78% of theoretical) of a colorless, viscous oil.

Elementary analysis:

Calculated:	C 33.23	H 2.61	F 55.85
Found:	C 33.09	H 2.78	F 55.71

b) 13,13,13,12,12,11,11,10,10,9,9,8,8,7,7,6,6-heptadecafluoro-3-oxa-tridecanic acid

9.0 g (15.56 mmol) of the title compound from Example 2e) are dissolved in 180 ml of trifluoracetic acid and are stirred at room temperature overnight. One evaporates to dryness in a vacuum. The residue is recrystallized from methanol/ether.

Yield: 7.80 g (96% of theoretical) of a colorless solid.

Elementary analysis:

Calculated:	C 27.60	H 1.35	F 61.85
Found:	C 27.48	H 1.49	F 61.66

c) Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-10,10,11,11,12,12,13,13,14,14,15,15,16,16,17,17,17-heptadecafluoro-heptadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

7.0 g (13.41 mmol) of the title compound from Example 2b) and 1.70 g (14.75 mmol) of N-hydroxysuccinimide are dissolved in a mixture consisting of 30 ml of dimethylformamide/20 ml of chloroform. At 0°C, one adds 3.04 g (14.75 mmol) of dicyclohexylcarbodiimide and one stirs for 1 hour at 0°C and then for 3 hours at room temperature. One again cools down to 0°C and one adds 4.48 g (44.25 mmol) of triethylamine/50 ml of 2-propanol. Then one adds 8.46 g (14.75 mmol) of gadolinium complex of 10-(3-amino-2-hydroxy-propyl)-1,4,7-

tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane dissolved in 40 ml of water and one stirs for 3 hours at room temperature. One evaporates to dryness, one absorbs the residue in a mixture consisting of 100 ml of methanol/30 ml of chloroform and one filters off the dicyclohexylurea. The filtrate is evaporated to dryness and is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-propanol/acetonitrile). /52

Yield: 11.8 g (75% of theoretical) of a colorless, glassy solid.

Water content: 8.2%.

T_1 relaxivity (L/mmol·sec) at 20 MHz, 37°C:

19 (water)

33 (human plasma)

Elementary analysis (related to anhydrous substance):

Calculated:	C 32.32	H 3.27	F 29.96	Gd 14.59	N 6.50
Found:	C 32.16	H 3.42	F 29.78	Gd 14.39	N 6.40

Example 3

a) 1,2-epoxy-4-oxa-1H,1H,2H,3H,3H,5H,5H,6H,6H-perfluoro-tetradecane

To a mixture consisting of 20 g (43.09 mmol) of 1H,1H,2H,2H-perfluorodecane-1-ol and 0.79 g (2.32 mmol) of tetrabutylammonium hydrogen sulfate in 200 ml of 60% caustic potash solution/100 ml of toluene, one drips in, while stirring forcefully at 10°C, 7.97 g (86.18 mmol) of epichlorhydrin, and one makes sure that the temperature of the reaction solution is no higher than 20°C. One

continues stirring for 2 hours at 15°C and one then, as described above, drips in 3.99 g (43.09 mmol) of epichlorhydrin. Then one keeps stirring at room temperature overnight. One adds 100 ml of methyl-tert.-butylether and one separates the aqueous phase. The latter is re-extracted twice with 50 ml each of toluene. The organic phases are combined, they are dried over magnesium sulfate and they are evaporated in a vacuum. The residue is chromatographed on silica gel (process agent: dichloromethane/hexane/acetone = 20/10/1).

Yield: 19.05 g (85% of theoretical) of a colorless oil.

Elementary analysis:

Calculated:	C 30.02	H 1.74	F 62.09
Found:	C 29.87	H 1.95	F 61.81

/53

b) 10-[-2-hydroxy-4-oxa-1H,1H,2H,3H,3H,5H,5H,6H,6H-perfluoro-tetradecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

To 12.0 g (34.60 mmol) of 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane in 50 ml of water, one adds 8.3 g (207.6 mmol) of sodium hydroxide. For this purpose, one drips in a solution consisting of 18.0 g (34.60 mmol) of the title compound from Example 3a) dissolved in 60 ml of n-butanol/60 ml of 2-propanol and one heats the solution overnight to 70°C. One evaporates in a vacuum until dryness, one absorbs the residue in 300 ml of water, and one sets at a pH of 3 with 3N hydrochloric acid. Then one extracts twice with 200 ml of n-butanol. The combined butanol phases are concentrated to dryness in a vacuum

and the residue is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-butanol/acetonitrile).

Yield: 26.61 g (79% of theoretical).

Water content: 11.0%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 37.42	H 4.07	F 37.27	N 6.47	
Found:	C 37.25	H 4.19	F 37.08	N 6.30	

c) Gadolinium complex of 10-[-2-hydroxy-4-oxa-1H,1H,2H,3H,3H,5H,5H,6H,6H-perfluoro-tetradecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

10 g (11.54 mmol) of the title compound from Example 3b) are dissolved in a mixture of 100 ml of water/50 ml of 2-propanol and one adds 2.09 g (5.77 mmol) of gadolinium oxide. One stirs for 3 hours at 80°C. The solution is filtered and is evaporated to dryness in a vacuum.

Yield: 12.48 g (quantitative) of a glassy solid.

Water content: 5.6%.

T_1 relaxivity (L/mmol·sec) at 20 MHz, 37°C:

15.2 (water)

27.5 (human plasma)

Elementary analysis (related to anhydrous substance): /54

Calculated:	C 31.77	H 3.16	F 31.64	Gd 15.40	N 5.49
Found:	C 31.55	H 3.30	F 31.49	Gd 15.28	N 5.35

Example 4

a) 1,2-epoxy-4-oxa-1H,1H,2H,3H,3H,5H,5H,6H,6H-perfluorododecane

To a mixture of 20 g (54.93 mmol) of 1H,1H,2H,2H-perfluoroctane-1-ol and 1.87 g (5.5 mmol) of tetrabutylammonium hydrogen sulfate in 200 ml of 60% aqueous caustic potash/100 ml of toluene, one drips in, while stirring forcefully at 10°C, 10.17 g (109.9 mmol) of epichlorhydrin, and one makes sure that the temperature of the reaction solution is no higher than 20°C. One continues stirring for 2 hours at 15°C and one then, as described above, drips in 5.08 g (54.93 mmol) of epichlorhydrin. Then one keeps stirring at room temperature overnight. One adds 100 ml of toluene and 100 ml of methyl-tert.-butylether and one separates the aqueous phase. The latter is re-extracted twice with 50 ml each of toluene. The organic phases are combined, they are dried over magnesium sulfate and they are evaporated in a vacuum. The residue is chromatographed on silica gel (process agent: dichloromethane/hexane/acetone = 20/10/1).

Yield: 19.15 g (83% of theoretical) of a colorless oil.

Elementary analysis:

Calculated:	C 31.44	H 2.16	F 58.78
Found:	C 31.40	H 2.29	F 58.55

b) 10-[-2-hydroxy-4-oxa-1H,1H,2H,3H,3H,5H,5H,6H,6H-perfluoro-tetradecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

To 14.84 g (42.84 mmol) of 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (DO3A) in 70 ml of water, one adds 10.3 g (257 mmol) of sodium hydroxide. For this purpose, one drips in a solution consisting of 18 g (42.84 mmol) of the title

compound from Example 4a) dissolved in 80 ml of n-butanol/60 ml of 2-propanol and one heats the solution overnight to a temperature of 70°C. One evaporates to dryness in a vacuum, one absorbs the residue in 300 ml of water and one sets a pH of 3 with 3N hydrochloric acid. Then one extracts twice with 200 ml of n-butanol. The combined butanol phases are concentrated to dryness in a vacuum and the residue is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-butanol/acetonitrile).

Yield: 27.4 g (75% of theoretical) of a glassy solid. /55

Water content: 10.1%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 39.17	H 4.60	F 32.22	N 7.31
Found:	C 39.05	H 4.85	F 32.05	N 7.19

c) Gadolinium complex of 10-[-2-hydroxy-4-oxa-1H,1H,2H,3H,3H,5H,5H,6H,6H-perfluoro-tetradecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

10 g (13.04 mmol) of the title compound from Example 4b) are dissolved in a mixture of 100 ml of water/50 ml of 2-propanol and one adds 2.36 g (6.52 mmol) of gadolinium oxide. One stirs for 3 hours at 80°C. The solution is filtered and is evaporated to dryness in a vacuum.

Yield: 12.77 g (quantitative) of a glassy solid.

Water content: 6.1%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 32.66	H 3.50	F 26.82	Gd 17.08	N 6.08

Found: C 32.43 H 3.69 F 26.67 Gd 16.85 N 5.91

Example 5

a) 9,9,9,8,8,7,7,6,6-nonafluoro-3-oxa-nonanic acid-t.-butylester

To a mixture of 20 g (75.73 mmol) of 1H,1H,2H,2H-perfluorohexane-1-ol and 2.57 g (7.57 mmol) of tetrabutylammonium hydrogen sulfate in 300 ml of 60% aqueous caustic potash/200 ml of toluene, one drips in, while stirring forcefully at 0°C, 29.54 g (151.5 mmol) of bromoacetic acid-tert.-butylester. One stirs for 1 hour at 0°C. One adds 100 ml of toluene, the aqueous phase is separated, and one extracts twice with 50 ml of toluene. The combined organic phases are dried over magnesium sulfate and are evaporated in a vacuum. The residue is chromatographed on silica gel (process agent: hexane/dichloromethane/acetone = 20/10/1)./56

Yield: 21.48 g (75% of theoretical) of a colorless oil.

Elementary analysis:

Calculated: C 38.11 H 4.00 F 45.21

Found: C 37.95 H 4.18 F 45.03

b) 9,9,9,8,8,7,7,6,6-nonafluoro-3-oxa-nonanic acid

20 g (52.88 mmol) of the title compound from Example 5a) are dissolved in 300 ml of trifluoracetic acid and are stirred overnight at room temperature. One evaporates to dryness in a vacuum. The residue is recrystallized from hexane/ether.

Yield: 14.82 g (87% of theoretical) of a colorless crystalline solid.

Elementary analysis:

Calculated: C 29.83 H 2.19 F 53.08

Found: C 29.71 H 2.40 F 52.90

c) Gadolinium complex of 10-[-2-hydroxy-4-aza-5-oxo-7-oxa-10,10,11,11,12,12,13,13,13-nonafluoro-tridecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

7.41 g (23.01 mmol) of the title compound from Example 5b) and 2.91 g (25.31 mmol) of N-hydroxysuccinimide are dissolved in a mixture of 40 ml of dimethylformamide/20 ml of chloroform. At 0°C, one adds 5.22 g (25.31 mmol) of dicyclohexylcarbodiimide and one stirs for 1 hour at 0°C, whereupon one continues stirring for 3 hours at room temperature. One again cools down to 0°C and one adds 6.98 g (69 mmol) of triethylamine/30 ml of 2-propanol. Then one dissolves 13.2 g (23.01 mmol) of gadolinium complex of 10-(3-amino-2-hydroxy-propyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane in 40 ml of water and one stirs for 3 hours at room temperature. One evaporates to dryness, one absorbs the residue in a mixture of 200 ml of methanol/50 ml of chloroform, and one filters off dicyclohexylurea. The filtrate is evaporated to dryness and is purified by RP chromatography (RP-18/process agent: gradient from water/n-propanol/acetonitrile). /57

Yield: 15.20 g (71% of theoretical) of a colorless, glassy solid.

Water content: 5.7%.

Elementary analysis (related to anhydrous substance):

Calculated: C 34.21 H 4.02 F 19.48 Gd 17.91 N 7.98

Found: C 34.09 H 4.18 F 19.31 Gd 17.74 N 7.87

Example 6

a) N-ethyl-N-(perfluoroctylsulfonyl)-aminoacetic acid-N-(2-aminoethyl)-amide

15 g (25.63 mmol) of the title compound from Example 1b) and 3.24 g (28.19 mmol) of N-hydroxysuccinimide are dissolved in 80 ml of dimethylformamide, and at 0°C, one adds 5.82 g (28.19 mmol) of dicyclohexylcarbodiimide. One stirs for 1 hour at 0°C and one continues stirring for 2 hours at room temperature. One filters from the precipitated dicyclohexylurea and one drips in the filtrate over a period of 30 minutes into a solution consisting of 46.21 g (768.9 mmol) ethylenediamine in 300 ml of dichloromethane. One stirs for 5 hours at room temperature. One adds 1000 ml of H_2O and one separates the organic phase. The latter is washed twice with 500 ml of water each, it is then dried over magnesium sulfate and is concentrated to dryness in a vacuum. Purification is done by chromatography on silica gel (process agent: dichloromethane/2-propanol = 15/1).

Yield: 11.79 g (75% of theoretical) of a colorless, wax-like solid.

Elementary analysis (related to anhydrous substance):

Calculated:	C 27.42	H 2.30	F 52.66	N 4.57	S 5.23
Found:	C 27.20	H 2.41	F 52.48	N 4.38	S 5.10

b) N-ethyl-N-(perfluoroctylsulfonyl)-amino acetic acid-N-[2-(bromacetyl)-aminoethyl]-amide

10 g (16.3 mmol) of the title compound from Example 6a) and 2.02 g (20 mmol) of triethylamine are dissolved in 40 ml of

dichloromethane. At -10°C over a period of 30 minutes, one drops in 3.29 g (16.3 mmol) of bromacetyl bromide and one stirs for 2 hours at 0°C. One pours the solution into 3 ml of 1N hydrochloric acid and one stirs thoroughly. The organic phase is separated, it is dried over magnesium sulfate and it is concentrated in a vacuum. The residue is chromatographed on silica gel (process agent: dichloromethane/acetone = 20/1). /58

Yield: 11.1 g (91% of theoretical) of a slightly yellow-colored, wax-like solid.

Elementary analysis (related to anhydrous substance):

Calculated: C 25.68 H 2.02 Br 10.68 F 43.16 N 5.62 S 4.29

Found: C 25.47 H 2.18 Br 10.45 F 43.29 N 5.47 S 4.10

c) 10-[2-oxo-3-aza-6-aza-7-oxo-9-aza-9-(perfluoroctylsulfonyl)-undecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

To 10 g (13.36 mmol) of the title compound found in Example 6b) in 180 ml of methanol, one adds 4.63 g (13.36 mmol) of 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (DO3A) and 18.5 g (133.6 mmol) of potassium carbonate. One boils for 12 hours under reflux. The inorganic salts are filtered off and the filtrate is evaporated to dryness. The residue is absorbed in 100 ml of water and is set at pH 3 with 5N hydrochloric acid. One extracts twice with 150 ml of n-butanol. The combined organic phases are concentrated to dryness in a vacuum and the residue is purified by means of RP chromatography (RP-18/process agent = gradient from water/n-butanol/acetonitrile).

Yield: 10.43 g (67% of theoretical) of a colorless solid.

Water content: 13.0%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 35.55	H 3.98	F 31.86	N 9.67	S 3.16
Found:	C 35.37	H 3.75	F 31.64	N 9.78	S 3.25

d) Gadolinium complex of 10-[-2-oxo-3-aza-6-aza-7-oxo-9-aza-9-(perfluoroctylsulfonyl)-undecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

10 g (9.86 mmol) of the title compound from Example 6c) are dissolved in a mixture of 50 ml of water/20 ml ethanol and 1.79 g (4.93 mmol) of gadolinium oxide are added. One stirs for 4 hours at 80°C. The solution is filtered and is evaporated to dryness in a vacuum. /59

Yield: 12.4% (quantitative).

Water content: 7.1%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 30.85	H 3.19	F 27.65	Gd 13.46	N 8.39	S 2.75
Found:	C 30.64	H 3.35	F 27.58	Gd 13.29	N 8.28	S 2.65

a) 1H,1H,2H,2H-perfluorodecane-1-ol-p-toluene sulfonic acid ester

To 30 g (64.64 mmol) of 1H,1H,2H,2H-perfluorodecane-1-ol in 300 ml of dichloromethane and 10.12 g (100 mmol) of triethylamine, one adds at 0°C 12.57 g (65.93 mmol) of p-toluene sulfonic acid chloride. One stirs for 2 hours at 0°C and then one continues stirring for 2 hours at room temperature. The solution is poured into 500 ml of cold 2N hydrochloric acid and

is stirred forcefully. The organic phase is separated, it is dried over magnesium sulfate and it is concentrated to dryness. The residue is recrystallized from a little bit of methanol.

Yield: 39.97% (95% of theoretical) of a colorless, crystalline powder.

Elementary analysis:

Calculated:	C 33.02	H 1.79	F 52.23	S 5.19
Found:	C 32.81	H 1.93	F 52.04	S 5.05

b) 10-[(1-hydroxymethyl-1-carboxyl)-methyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

To a solution of 20 g (57.78 mmol) of 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (DO3A), 31.21 g (780 mmol) of sodium hydroxide and 2 g (12 mmol) of potassium iodide in 100 ml of dimethylformamide, one adds 37.2 g (173.4 mmol) of 2-chloro-3-benzyloxy-propanic acid and one stirs for 3 days at 60°C. One evaporates down to dryness and one dissolves the residue in 300 ml of water. Then one adjusts for a pH of 3 with 3N of hydrochloric acid and one extracts twice with 250 ml of dichloromethane each. To the water phase, one now adds 4 g of palladium catalyst (10% Pd/C) and one hydrates for 5 hours at 60°C. The catalyst is filtered off and the filtrate is concentrated to dryness. The residue is filtered off by means of RP chromatography (RP-18/process agent: gradient from water/2-propanol/acetonitrile). /60

Yield: 5.92 g (21% of theoretical related to DO3A) of a colorless, glassy solid.

Water content: 11.1%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 47.00	H 6.96	N 12.90
Found:	C 46.81	H 6.78	N 12.99

c) 10-[1-hydroxymethyl-1-(methoxycarbonyl)-methyl]-1,4,7-tris(methoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane

Into 200 ml of methanol at 0°C, one drips in 9.53 g (80 mmol) of thionyl chloride. Then one adds 5.8 g (13.35 mmol) of the title compound from Example 7b) and one stirs for 1 hour at 0°C. Then one heats for 6 hours to 60°C. One evaporates to dryness, one absorbs the residue in 150 ml of methylene chloride and one extracts three times with 200 ml each of 8% aqueous soda solution. The organic phase is dried over magnesium sulfate and is evaporated to dryness. One gets 6.09 g (93% of theoretical) of the title compound as a slightly yellow-colored oil.

Elementary analysis:

Calculated:	C 51.42	H 7.81	N 11.42
Found:	C 51.20	H 7.95	N 11.28

d) 10-[1-(methoxycarbonyl)-3-oxa-1H,2H,2H,4H,4H,5H,5H-perfluorotridecyl]-1,4,7-tris(methoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane

To 6 g (12.23 mmol) of the title compound from Example 7c) in 40 ml of dimethylformamide, one adds 0.44 g (14.68 mmol) of sodium hydride (80% suspension in mineral oil) and one stirs for 30 minutes at -10°C. Then one adds 8.32 g (13.45 mmol) of the title compound from Example 7a) and one stirs at room temperature

for 8 hours. Now one cautiously adds 400 ml of ice water and one extracts twice with 300 ml each of acetic acid ethyl ester. The combined acetic acid ethyl ester phases are washed with saturated aqueous common salt solution and are dried over magnesium sulfate. One evaporates to dryness in a vacuum and one chromatographs the residue on silica gel (process agent: dichloromethane/methanol = 20/1). /61

Yield: 7.68% (67% of theoretical) of a viscous yellow oil.

Elementary analysis:

Calculated:	C 39.75	H 4.41	F 34.48	N 5.98
Found:	C 39.58	H 4.60	F 34.27	N 5.75

e) 10-[1-carboxy-3-oxa-1H,2H,2H,4H,4H,5H,5H-perfluorotridecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

7.5 g (8.01 mmol) of the title compound from Example 7d) are suspended in a mixture of 50 ml of water/30 ml of ethanol and then one adds 3.84 g (96 mmol) of sodium hydroxide. One cools down to room temperature and one adjusts a pH of 3 with 3N of hydrochloric acid. One evaporates to dryness in a vacuum and one purifies the residue by means of RP chromatography RP-18/process agent = gradient from water/n-butanol/acetonitrile).

Yield: 6.84% (87% of theoretical) of a glassy solid.

Water content: 10.3%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 36.83	H 3.78	F 36.68	N 6.36
Found:	C 36.67	H 3.90	F 36.49	N 6.25

f) Gadolinium complex of 10-[1-carboxy-3-oxa-1H,2H,2H,4H,4H,5H,5H-perfluorotridecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (as sodium salt)

6 g (6.81 mmol) of the title compound from Example 7e) are suspended in 80 ml of water and one adds 1.23 g (3.4 mmol) gadolinium oxide. One heats for 3 hours to 90°C. One allows the mixture to cool down to room temperature and one adjusts a pH of 7.2 with 2N caustic soda. The solution is filtered and is then freeze dried. /62

Yield: 7.83 g (quantitative) of a colorless, flaky powder.

Water content: 8.1%.

Elementary analysis (related to anhydrous substance):

Calculated: C 30.69 H 2.77 F 30.56 Gd 14.88 N 5.30 Na 2.18

Found: C 30.48 H 2.85 F 30.37 Gd 14.69 N 5.17 Na 1.95

Example 8

a) 2H,2H-perfluoroctanal

30 g (82.4 mmol) of 1H,1H,2H,2H-perfluoroctane-1-ol is dissolved in 500 ml of dichloromethane and one adds 17.76 g (82.4 mmol) of pyridinium chlorochromate. One stirs overnight at room temperature. The solution is filtered over a short column filled with (neutral) aluminum oxide; the filtrate is evaporated to dryness and the residue is chromatographed on silica gel (process agent: dichloromethane/hexane/acetone = 10/10/1).

Yield: 26.55 g (89% of theoretical) of a wax-like solid.

Elementary analysis:

Calculated:	C 26.54	H 0.84	F 68.21		
Found:	C 26.47	H 1.05	F 68.10		

b) 2-amino-2H,3H,3H-perfluorononanic acid as hydrochloride

7.04 g (143.6 mmol) of sodium cyanide and 8.45 g (157 mmol) of ammonium chloride are dissolved in 30 ml of water. To this solution, one adds 40 ml of ethanol and 26 g (71.8 mmol) of the title compound from Example 8a). One heats for 2 hours at a temperature of 45°C. One now adds 300 ml of water and one extracts three times with 200 ml of benzene each. The combined benzene phases are washed three times with 200 ml of water each and the organic phase is evaporated to dryness in a vacuum. The residue is absorbed in 100 ml of 6N aqueous hydrochloric acid/50 ml of methanol and is heated for 2 hours under reflux. One evaporates to dryness in a vacuum. The residue is recrystallized from a little bit of 2-propanol/methyl-tert.-butylether. /63

Yield: 11.15 g (35% of theoretical) of a crystalline solid.

Elementary analysis:

Calculated:	C 24.37	H 1.59	Cl 7.99	F 55.68	N 3.16
Found:	C 24.15	H 1.72	Cl 7.65	F 55.51	N 3.05

c) 2-[(N-benzoyloxycarbonyl)-triglycidyl]-amino-2H,3H,3H-perfluorononanic acid

8.37 g (24.8 mmol) of N-benzoylcarbonyl-triglycine and 3.14 g (27.28 mmol) of N-hydroxysuccinimide are dissolved in 80 ml of dimethylformamide, and at 0°C, one adds 5.63 g (27.28 mmol) of dicyclohexylcarbodiimide. One continues to stir for 1 hour at 0°C after which one continues for another 2 hours at room

temperature. One cools down to 0°C, one adds 7.53 g (74.4 mmol) of triethylamine and 11 g (24.8 mmol) of the title compound from Example 8b) and one then stirs overnight at room temperature. One evaporates in a vacuum to dryness, one absorbs the residue in 300 ml of 5% aqueous citric acid and one extracts three times with 200 ml each of acetic acid ethyl ester. The combined organic phases are dried over magnesium sulfate and are evaporated to dryness in a vacuum. The residue is chromatographed on silica gel (process agent: dichloromethane/n-propanol = 20/1).

Yield: 11.83% (67% of theoretical) of a colorless, scale-like solid.

Elementary analysis:

Calculated:	C 38.78	H 2.97	F 34.67	N 7.86
Found:	C 38.59	H 2.85	F 34.48	N 7.91

d) 2-[triglycidyl]-amino-2H,3H,3H-perfluorononanic acid

11.5 g (16.14 mmol) of the title compound from Example 8c) is dissolved in 200 ml of 2-propanol and one adds 3 g of palladium catalyst (10% Pd/C). One hydrates overnight at room temperature. One filters off the catalyst and the filtrate is evaporated to dryness. /64

Yield: 9.33 g (quantitative) of a colorless solid.

Elementary analysis:

Calculated:	C 31.15	H 2.61	F 42.71	N 9.69
Found:	C 31.29	H 2.80	F 42.53	N 9.48

e) 2-(1H,1H-perfluoroheptyl)-1,4,7,10-tetraaza-3,6,9,12-tetraoxo-cyclododecane

9.2 g (15.91 mmol) of the title compound from Example 8d) are dissolved in 1000 ml of dimethylformamide and 3.93 g (15.91 mmol) of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline. One stirs for 3 days at room temperature. One evaporates to dryness and the residue is chromatographed on silica gel (process agent: dichloromethane/2-propanol = 20/1).

Yield: 4.54 g (51% of theoretical) of a wax-like solid.

Elementary analysis:

Calculated:	C 32.16	H 2.34	F 44.08	N 10.00
Found:	C 32.05	H 2.47	F 43.87	N 9.89

f) 2-(1H,1H-perfluoroheptyl)-1,4,7,10-tetraazacyclododecane (as tetrahydrochloride)

To 4.4 g (7.85 mmol) of the title compound from Example 8e), one adds 200 ml of 1 M borane-tetrahydrofurane complex solution and one boils for 2 days under reflux. One evaporates to dryness in a vacuum and one absorbs the residue in 50 ml of concentrated hydrochloric acid. One adds 100 ml of ethanol and one boils for 8 hours under reflux. One evaporates to dryness in a vacuum and the residue is recrystallized from ethanol.

Yield: 4.75 g (93% of theoretical) of a colorless, crystalline powder.

Elementary analysis: /65

Calculated:	C 27.71	H 3.88	Cl 21.81	F 37.99	N 8.62
Found:	C 27.65	H 3.95	Cl 21.40	F 37.69	N 8.41

g) 2-(1H,1H-perfluoroheptyl)-1,4,7,10-tetra(carboxymethyl)-1,4,7,10-tetraazacyclododecane

4.6 g (7.07 mmol) of the title compound from Example 8f) and 4.0 g (42.4 mmol) of chloroacetic acid are dissolved in 40 ml of water and the pH is set at 10 by adding 30% aqueous caustic potash solution. One heats for 8 hours to 70°C and one keeps the pH value between 8 and 10 (by adding 50% aqueous caustic potash solution). The solution is cooled down to room temperature, it is set at a pH of 2 with concentrated hydrochloric acid and it is evaporated to dryness. The residue is absorbed in 150 ml of methanol, the salts are filtered off and the filtrate is evaporated to dryness in a vacuum. The residue is purified by means of RP-18 chromatography (RP-18/process agent: gradient from water/2-propanol/acetonitrile).

Yield: 5.03 g (87% of theoretical) of a glassy solid.

Water content: 10.1%.

Elementary analysis:

Calculated:	C 37.51	H 3.97	F 33.53	N 7.61
Found:	C 37.35	H 4.12	F 33.40	N 7.45

h) Gadolinium complex of 2-(1H,1H-perfluoroheptyl)-1,4,7,10-tetra(carboxymethyl)-1,4,7,10-tetraazacyclododecane (as sodium salt)

4.5 g (6.11 mmol) of the title compound from Example 8g) is suspended in 100 ml of water and one adds 1,107 g (3.05 mmol) of gadolinium complex. One heats for 3 hours to 90°C. One cools down to room temperature and one sets for a pH of 7.2 with 2N of

caustic soda. The solution is filtered and it is then freeze dried.

Yield: 6.03 g (quantitative) of a colorless powder.

Water content: 7.5%.

Elementary analysis (related to anhydrous substance): /66

Calculated: C 30.23 H 2.87 F 27.03 Gd 17.21 N 6.13 Na 2.52

Found: C 30.10 H 3.05 F 26.81 Gd 17.15 N 5.95 Na 2.30

Example 9

a) 10-[2-hydroxy-1H,1H,2H,3H,3H-perfluorononyl]-1,4,7-tris(carboyxmethyl)-1,4,7,10-tetraazacyclododecane

To 15 g (43.3 mmol) of 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane in 50 ml of water, one adds 13.85 g (346.4 mmol) of sodium hydroxide. For this purpose, one drips in a solution consisting of 27.68 g (64.95 mmol) of 1,2-epoxy-1H,1H,2H,3H,3H-perfluorononane dissolved in 50 ml of n-butanol/50 ml of 2-propanol and one heats the solution to 80°C overnight. One evaporates to dryness in a vacuum, one absorbs the residue in 200 ml of water and one sets a pH of 3 with 3N hydrochloric acid. Then one extracts twice with 200 ml of n-butanol. The combined butanol phases are concentrated to dryness in a vacuum and the residue is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-butanol/acetonitrile).

Yield: 30.34 g (78% of theoretical) of a glassy solid.

Water content: 13.7%.

Elementary analysis (related to anhydrous substance):

Calculated: C 37.32 H 4.04 F 36.89 N 7.25

Found: C 37.15 H 4.21 F 36.70 N 7.19

b) Gadolinium complex of 10-(2-hydroxy-1H,1H,2H,3H,3H-perfluorononyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

10 g (12.94 mmol) of the title compound from Example 9a) is dissolved in 100 ml of water/50 ml of ethanol and one adds 2.34 g (6.47 mmol) of gadolinium complex. One stirs for 3 hours at 80°C. The solution is filtered and is evaporated to dryness in a vacuum.

Yield: 13.16 g (quantitative) of a colorless, glassy solid.

Water content: 9.1%. /67

Calculated: C 31.11 H 3.05 F 30.75 Gd 16.97 N 6.05

Found: C 31.01 H 3.19 F 30.55 Gd 16.71 N 5.88

Example 10

a) 9H,9H,10H,11H,12H,12H-perfluoreicos-10-ene

24.77 g (52.26 mmol) of 1H,1H,2H,2H-perfluorodecyl-1-iodide and 13.71 g (52.26 mmol) of triphenylphosphine are heated to 70°C in 500 ml of acetone while stirring. The initially clear solution quickly becomes milky cloudy and separates the colorless phosphonium salt. One filters the phosphonium salt off, one dries at a vacuum at 40°C.

Yield: 38.9 g (89% of theoretical).

This phosphonium salt is used without purification directly in the following reaction: To the above-produced phosphonium salt, 38.9 g (46.5 mmol) in 250 ml of dichloromethane, one adds 5.22 g (46.5 mmol) of potassium-tert.-butylate, 0.20 g (0.75

mmol) of 18-krone-6 and 19.54 g (42.54 g (42.28 mmol) of 2H,2H-perfluorodecanal and one stirs for 10 hours at room temperature. One evaporates to dryness and one chromatographs the residue on silica gel (process agent: dichloromethane/n-hexane/diethylether = 10/20/1).

Yield: 30.3 g (65% of theoretical related to the iodide used) of a colorless, wax-like solid.

Elementary analysis:

Calculated:	C 26.92	H 0.68	F 72.40
Found:	C 26.81	H 0.79	F 72.20

b) 10,11-epoxy-9H,9H,10H,11H,12H,12H-perfluoreicosane

To 25 g (28.02 mmol) of the title compound from Example 10a) dissolved in 250 ml dichloromethane at 0°C, one adds 10.47 g (36.42 mmol) of 3-chloroperoxybenzoic acid (about 60%) and one stirs overnight at room temperature. One adds 300 ml of 5% aqueous sodium carbonate solution and one stirs thoroughly. The organic phase is separated, it is dried over magnesium sulfate and it is evaporated to dryness in a vacuum. The residue is chromatographed on silica gel (process agent: hexane/dichloromethane/diethylether = 10/10/1). /68

Yield: 24.17 g (95% of theoretical of a colorless solid.

Elementary analysis:

Calculated:	C 26.45	H 0.67	F 71.12
Found:	C 26.25	H 0.88	F 71.35

c) 10-[1-(1H,1H-perfluorononyl)-2-hydroxy-1H,2H,3H,3H-perfluorundecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododo

To 7.63 g (22.02 mmol) of 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane in 35 ml of water, one adds 7.04 g (0.176 mmol) of sodium hydroxide. For this purpose, one drips in a solution consisting of 20 g (22.02 mmol) of the title compound from Example 10b) dissolved in 50 ml of n-butanol/40 ml of 2-propanol and one heats the solution overnight to 120°C in the autoclave. One evaporates to dryness in a vacuum, one absorbs the residue in 200 ml of water and one adjusts a pH of 3 with 3N hydrochloric acid. Then one extracts twice with 300 ml of n-butanol. The combined butanol phases are concentrated to dryness in a vacuum and the residue is purified by means of RP chromatography RP-18/process agent: gradient from water/n-butanol/acetonitrile).

Yield: 9.79 g (31% of theoretical) of a colorless, glassy solid.

Water content: 12.5%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 32.55	H 2.57	F 51.49	N 4.47
Found:	C 32.38	H 2.75	F 51.29	N 4.28

d) Gadolinium complex of 10-(1-1H,1H-perfluorononyl]-2-hydroxy-1H,2H,3H,3H-perfluorundecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

8 g (6.38 mmol) of the title compound from Example 10c) is dissolved in 50 ml of water/40 ml of ethanol/20 ml of chloroform

and one adds 1.16 g (3.19 mmol) of gadolinium complex. One stirs for 4 hours at 90°C in an autoclave. The solution is filtered and is evaporated to dryness in a vacuum. /69

Yield: 9.47 g (quantitative) of a glassy solid.

Water content: 5.2%

Elementary analysis (related to anhydrous substance):

Calculated:	C 28.99	H 2.07	F 45.85	Gd 11.16	N 3.98
Found:	C 28.81	H 2.19	F 45.71	Gd 11.03	N 4.12

Example 11

a) 7H,7H,8H,9H,10H,10H-perfluorohexadec-8-ene

18.7 g (50 mmol) of 1H,1H,2H,2H-perfluoroctyl-1-iodide and 13.11 g (50 mmol) of triphenylphosphine are heated to 70°C in 400 ml of acetone while stirring. The initially clear solution quickly becomes milky cloudy and separates the colorless phosphonium salt. One filters the phosphonium salt, one dries in a vacuum at 40°C.

Yield: 28.95 g (91% of theoretical).

This phosphonium salt is used without purification directly in the following reaction: To the phosphonium salt produced above, 28.95 g (45.5 mmol) in 200 ml of dichloromethane, one adds 5.05 g (45.5 mmol) of potassium-tert.-butylate, 0.20 g (0.75 mmol) of 18-krone-6 and 14.98 g (41.36 mmol) of the title compound from Example 8a) and one stirs for 10 hours at room temperature. One evaporates to dryness and one chromatographs the residue on silica gel (process agent: dichloromethane/n-hexane/diethylether = 10/20/1).

Yield: 19.65 g (61% of theoretical) of a colorless, wax-like solid.

Elementary analysis:

Calculated:	C 22.38	H 0.94	F 76.69
Found:	C 22.20	H 0.99	F 76.51

b) 8,9-epoxy-7H,7H,8H,9H,10H,10H-perfluorohexadecane /70

To 19 g (29.5 mmol) of the title compound from Example 11a) dissolved in 200 ml of dichloromethane, one adds at 0°C 11.03 g (38.35 mmol) of 3-chlorperoxybenzoic acid (about 60%) and one stirs overnight at room temperature. One adds 300 ml of 5% aqueous sodium carbonate solution and one stirs thoroughly. The organic phase is separated, it is dried over magnesium sulfate and it is evaporated to dryness in a vacuum. The residue is chromatographed on silica gel (process agent: n-hexane/dichloromethane/diethylether = 10/10/1).

Yield: 19.43 g (93% of theoretical) of a colorless solid.

Elementary analysis:

Calculated:	C 27.14	H 0.85	F 69.75
Found:	C 27.01	H 0.97	F 69.60

c) 10-[1-(1H,1H-perfluoroheptyl)-2-hydroxy-1H,2H,3H,3H-perfluorononyl]-1,4,7,-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

To 9.3 g (26.83 mmol) of 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane dissolved in 50 ml of water, one adds 8.59 m (214.6 mmol) of sodium hydroxide. For this purpose, one drips in a solution consisting of 19 g (26.83 mmol) of the title

compound from Example 11b) dissolved in 70 ml of n-butanol/60 ml of 2-propanol and one heats the solution overnight to 120°C in the autoclave. One evaporates to dryness in a vacuum, one absorbs the residue in 200 ml of water and one adjusts a pH of 3 with 3N hydrochloric acid. Then one extracts twice with 300 ml of n-butanol. The combined butanol phases are concentrated to dryness in a vacuum and the residue is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-butanol/acetonitrile).

Yield: 9.4 g (29% of theoretical) of a glassy solid.

Water content: 12.7%.

Elementary analysis (related to anhydrous substance): /71

Calculated:	C 34.17	H 3.06	F 46.84	N 5.31	
Found:	C 33.98	H 3.18	F 46.65	N 5.20	

d) Gadolinium complex of 10-(1-1H,1H-perfluoroheptyl]-2-hydroxy-1H,2H,3H,3H-perfluorononyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

9 g (8.53 mmol) of the title compound from Example 11c) is dissolved in 60 ml of water/40 ml of ethanol/30 ml of chloroform and one adds 1.54 g (4.27 mmol) of gadolinium complex. One stirs for 4 hours at 90°C in an autoclave. The solution is filtered and is evaporated to dryness in a vacuum.

Yield: 11.45 g (quantitative) of a colorless, glassy solid.

Water content: 10.2%

Elementary analysis (related to anhydrous substance):

Calculated:	C 29.81	H 2.42	F 40.86	Gd 13.01	N 4.63

Found: C 29.60 H 2.60 F 40.63 Gd 12.84 N 4.51

Example 12

a) 7,12-dioxa-5H,5H,6H,6H,8H,8H,9H,10H,11H,11H,13H,13H,14H,14H-perfluoroctadec-9-ene

30 g (91.74 mmol) of 1H,1H,2H,2H-perfluorohexyl-1-bromide is dissolved in 100 ml of toluene and one then adds 3.23 g (36.7 mmol) of cis-1,4-butene-diol and 1 g (2.95 mmol) of tetrabutylammonium hydrogen sulfate. One cools down to 0°C and one adds 16 g (400 mmol) of finely powdered sodium hydroxide. Then one stirs for 1 hour at 0°C and overnight at room temperature. One filters off the solid, one washes the filtrate twice with 200 ml of water each, one dries the organic phase over magnesium sulfate and one then evaporates to dryness in a vacuum. The residue is chromatographed on silica gel (process agent: dichloromethane/n-hexane/acetone = 15/15/1).

Yield: 11.71 g (55% of theoretical related to diol) of a wax-like solid.

Elementary analysis: /72

Calculated: C 33.12 H 2.43 F 58.93

Found: C 33.05 H 2.61 F 58.73

b) 9,10-epoxy-7,12-dioxa-5H,5H,6H,6H,8H,8H,9H,10H,11H,11H,13H,13H,14H,14H-perfluoroctadecane

To 11 g (18.96 mmol) of the title compound from Example 12a) dissolved in 100 ml of dichloromethane, one adds at 0°C 7.08 g (24.64 mmol) of 3-chlorperoxybenzoic acid (about 60%) and one

stirs overnight at room temperature. One adds 150 ml of 5% aqueous sodium carbonate solution and one stirs thoroughly. The organic phase is separated, it is dried over magnesium sulfate and it is evaporated to dryness in a vacuum. The residue is chromatographed on silica gel (process agent: n-hexane/dichloromethane/diethylether = 10/10/1).

Yield: 10.74 g (95% of theoretical) of a colorless solid.

Elementary analysis:

Calculated:	C 32.23	H 2.37	F 57.35
Found:	C 32.13	H 2.51	F 57.20

c) 10-[1-(2-oxa-1H,1H,3H,3H,4H,4H-perfluoroctyl)-2-hydroxy-4-oxa-1H,2H,3H,3H,5H,5H,6H,6H-perfluorodecyl]-1,4,7,-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

To 613 g (17.61 mmol) of 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane dissolved in 40 ml of water, one adds 5.63 m (141 mmol) of sodium hydroxide. For this purpose, one drips in a solution consisting of 10.5 g (17.61 mmol) of the title compound from Example 12b) dissolved in 50 ml of n-butanol/40 ml of 2-propanol and one heats the solution overnight to 120°C in the autoclave. One evaporates to dryness in a vacuum, one absorbs the residue in 200 ml of water and one adjusts a pH of 3 with 3N hydrochloric acid. Then one extracts twice with 300 ml of n-butanol. The combined butanol phases are concentrated to dryness in a vacuum and the residue is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-butanol/acetonitrile).

Yield: 4.96 g (27% of theoretical) of a colorless, glassy solid.

Water content: 9.7%. /73

Elementary analysis (related to anhydrous substance):

Calculated:	C 38.27	H 4.17	F 36.32	N 5.95	
Found:	C 38.12	H 4.20	F 36.20	N 5.81	

d) Gadolinium complex of 10-[1-(2-oxa-1H,1H,3H,3H,4H,4H-perfluoroctyl]-2-hydroxy-4-oxa-1H,2H,3H,3H,5H,5H,6H,6H-perfluorodecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

4.7 g (5 mmol) of the title compound from Example 12c) is dissolved in 30 ml of water/30 ml of ethanol/20 ml of chloroform and one adds 0.90 g (2.5 mmol) of gadolinium complex. One stirs for 3.5 hours at 90°C in an autoclave. The solution is filtered and is evaporated to dryness in a vacuum.

Yield: 5.89 g (quantitative) of a colorless, glassy solid.

Water content: 7.1%

Elementary analysis (related to anhydrous substance):

Calculated:	C 32.88	H 3.31	F 31.21	Gd 14.35	N 5.11
Found:	C 32.67	H 3.45	F 31.04	Gd 14.18	N 5.02

Example 13

a) 1-phenyl-2,6-dioxa-1H,1H,3H,3H,4H,5H,5H,7H,7H,8H,8H-perfluorohexadecane-4-ol

To 7.14 g (39.2 mmol) of glycerin-1-monobenzylether and 25 g (43.55 mmol) of 1H,1H,2H,2H-perfluorodecyl-1-iodide in 100 ml of toluene, one adds 1 g (2.94 mmol) of tetrabutylammonium hydrogen

sulfate and 15.6 g (390 mmol) of finely powdered sodium hydroxide. One stirs for 24 hours at room temperature. One separates the organic phase from the solid and one washes twice with 5% aqueous hydrochloric acid each. The organic phase is dried over magnesium sulfate and it is evaporated to dryness in a vacuum. The residue is chromatographed on silica gel (process agent: n-hexane/acetone = 15/1).

Yield: 19.95 g (81% of theoretical) of a colorless oil. /74

Elementary analysis:

Calculated:	C 38.23	H 2.73	F 51.40
Found:	C 38.10	H 2.89	F 51.25

b) 1-phenyl-4-(decyloxy)-2,6-dioxa-

1H,1H,3H,3H,4H,5H,5H,7H,7H,8H,8H-perfluorohexadecane

To 19.5 g (31.03 mmol) of the title compound from Example 13a) dissolved in 100 ml of dimethylformamide, one adds in portions 1.12 g (37.24 mmol) of sodium hydride (80% suspension in mineral oil) and one stirs for 2 hours at room temperature. Then one adds 8.24 g (37.24 mmol of n-decyl bromide and one stirs overnight at 50°C. One adds 150 ml of ice water and one extracts twice with 150 ml each of acetic acid ethyl ester. The combined organic phases are washed twice with 150 ml of water each, they are dried over magnesium sulfate and they are evaporated to dryness in a vacuum. The residue is chromatographed on silica gel (process agent: n-hexane/acetone = 20/1).

Yield: 22.66 g (95% of theoretical) of a wax-like solid.

Elementary analysis:

Calculated: C 46.88 H 4.85 F 42.02

Found: C 46.64 H 4.97 F 41.87

c) 2-(decyloxy)-4-oxa-1H,1H,2H,3H,3H,5H,5H,6H,6H-perfluorotetradecane-1-ol

20 g (26.02 mmol) of the title compound from Example 13b) is dissolved in 200 ml of isopropanol and 3 g of palladium catalyst (10% Pd/C). One hydrates overnight at room temperature. The catalyst is filtered off and the filtrate is concentrated to dryness in a vacuum.

Yield: 17.65 g (quantitative) of a colorless solid.

Elementary analysis: /75

Calculated: C 40.72 H 4.61 F 47.60

Found: C 40.55 H 4.76 F 47.43

d) 1,2-epoxy-4-oxa-6-(decyloxy)-8-oxa-1H,1H,2H,3H,3H,5H,5H,6H,7H,7H,9H,9H,10H,10H-perfluoroctadecane

To a mixture of 17 g (25.06 mmol) of the title compound from Example 13c) and 2 g (5.89 mmol) of tetrabutylammonium hydrogen sulfate in 300 ml of 60% aqueous caustic potash solution/100 ml of toluene, one drips in, while stirring forcefully at 10°C, 9.25 g (100 mmol) of epichlorhydrin, and one makes sure that the temperature of the reaction solution does not exceed 20°C. One continues stirring for 2 hours at 15°C and one then, as described above, 4.63 g (50 mmol) of epichlorhydrin. Then one stirs overnight at room temperature. One adds 100 ml of toluene and methyl-tert.-butylether and one separates the aqueous phase. The

latter is re-extracted twice with 100 ml of toluene each. The organic phases are combined, they are dried over magnesium sulfate and they are evaporated in a vacuum. The residue is chromatographed on silica gel (process agent: dichloromethane/hexane/acetone = 20/10/1).

Yield: 14.91 g (81% of theoretical) of a colorless solid.

Elementary analysis:

Calculated:	C 42.51	H 4.80	F 43.97
Found:	C 42.37	H 4.96	F 43.68

e) 10-[2-hydroxy-4,8-dioxa-6-(decyloxy)-1H,1H,2H,3H,3H,5H,5H,6H,7H,7H,9H,9H,10H,10H-perfluoroctadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

To 6.6 g (19.06 mmol) of 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane in 60 ml of water, one adds 6.11 g (152.8 mmol) of sodium hydroxide. For this purpose, one drips in a solution consisting of 14 g (19.06 mmol) of the title compound from Example 13d) dissolved in 80 ml of n-butanol/40 ml of 2-propanol and one heats the solution overnight to 80°C in the autoclave. One evaporates to dryness in a vacuum, one absorbs the residue in 200 ml of water and one adjusts a pH of 3 with 3N hydrochloric acid. Then one extracts twice with 300 ml of n-butanol. The combined butanol phases are concentrated to dryness in a vacuum and the residue is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-butanol/acetonitrile). /76

Yield: 17.88 g (76% of theoretical) of a glassy solid.

Water content: 12.5%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 44.49	H 5.60	F 29.91		N 5.19
Found:	C 44.31	H 5.75	F 29.70		N 5.03

f) Gadolinium complex of 10-[2-hydroxy-4,8-dioxa-6-(decyloxy)-1H,1H,2H,3H,3H,5H,5H,6H,7H,7H,9H,9H,10H,10H-perfluoroctadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

10 g (9.26 mmol) of the title compound from Example 13e) is dissolved in 30 ml of water/100 ml of ethanol/30 ml of chloroform and one adds 1.68 g (4.63 mmol) of gadolinium complex. One stirs for 3.5 hours at 90°C in an autoclave. The solution is filtered and is evaporated to dryness in a vacuum.

Yield: 12.39 g (quantitative) of a colorless, glassy solid.

Water content: 7.8%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 38.93	H 4.66	F 26.17	Gd 12.74	N 4.54
Found:	C 38.71	H 4.82	F 26.01	Gd 12.55	N 4.38

Example 14

a) 1-phenyl-2-oxa-4,4,4-tris(2-oxa-1H,1H,3H,3H,4H,4H-perfluorodecyl)-butane

To 4.24 g (18.74 mmol) of pentaerythrite-monobenzylether and 40 g (93.7 mmol) of 1H,1H,2H,2H-perfluoroctyl-1-bromide in 150 ml of toluene, one adds 2 g (5.89 mmol) of tetrabutylammonium hydrogen sulfate and 22.48 g (562 mmol) of finely powdered sodium

hydroxide. One stirs for 24 hours at room temperature. One separates the organic phase from the solid and one washes twice with 5% aqueous hydrochloric acid each. The organic phase is dried over magnesium sulfate and it is evaporated to dryness in a vacuum. The residue is chromatographed on silica gel (process agent: n-hexane/acetone = 25/1). /77

Yield: 14.45 g (61% of theoretical related to benzyl ether) of a colorless, wax-like solid.

Elementary analysis:

Calculated:	C 34.19	H 2.15	F 58.59
Found:	C 34.02	H 2.31	F 58.41

b) 2,2,2-tris(2-oxa-1H,1H,3H,3H,4H,4H-perfluorodecyl)-ethane-1-ol

14 g (11.07 mmol) of the title compound from Example 14a) is dissolved in 100 ml of isopropanol/100 ml of tetrahydrofurane and 3 g of palladium catalyst (10% Pd/C). One hydrates overnight at room temperature. The catalyst is filtered off and the filtrate is concentrated to dryness in a vacuum.

Yield: 13 g (quantitative) of a colorless solid.

Elementary analysis:

Calculated:	C 29.66	H 1.80	F 63.09
Found:	C 29.45	H 1.97	F 62.91

c) 1,2-epoxy-4-oxa-6,6,6-tris(2-oxa-1H,1H,3H,3H,4H,4H-perfluorodecyl)-hexane

To a mixture of 12.5 g (10.04 mmol) of the title compound from Example 14b) and 1 g (2.95 mmol) of tetrabutylammonium

hydrogen sulfate in 150 ml of 60% aqueous caustic potash solution/50 ml of toluene, one drips in, while stirring forcefully at 10°C, 3.94 g (42.57 mmol) of epichlorhydrin, and one makes sure that the temperature of the reaction solution does not exceed 20°C. One continues stirring for 2 hours at 15°C and one then, as described above, 1.97 g (21.29 mmol) of epichlorhydrin. Then one stirs overnight at room temperature. One adds 100 ml of toluene and 100 ml of methyl-tert.-butylether and one separates the aqueous phase. The latter is re-extracted twice with 50 ml of toluene each. The organic phases are combined, they are dried over magnesium sulfate and they are evaporated in a vacuum. The residue is chromatographed on silica gel (process agent: dichloromethane/hexane/acetone = 20/10/1)./78

Yield: 8.12 g (62% of theoretical) of a colorless solid.

Elementary analysis:

Calculated:	C 31.24	H 2.05	F 60.22
Found:	C 31.09	H 2.19	F 60.10

d) 10-[2-hydroxy-4-oxa-6,6,6-tris(2-oxa-1H,1H,3H,3H,4H,4H,-perfluorodecyl)-hexyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

To 2.25 g (6.50 mmol) of 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane in 30 ml of water, one adds 2.08 g (52 mmol) of sodium hydroxide. For this purpose, one drips in a solution consisting of 8.0 g (6.50 mmol) of the title compound from Example 14c) dissolved in 50 ml of n-butanol/40 3 ml of 2-propanol and one heats the solution overnight to 100°C in the

autoclave. One evaporates to dryness in a vacuum, one absorbs the residue in 200 ml of water and one adjusts a pH of 3 with 3N hydrochloric acid. Then one extracts twice with 100 ml of n-butanol. The combined butanol phases are concentrated to dryness in a vacuum and the residue is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-butanol/acetonitrile).

Yield: 7.79 g (67% of theoretical) of a colorless, glassy solid.

Water content: 11.9%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 35.06	H 3.20	F 47.02	N 3.56
Found:	C 34.90	H 3.38	F 46.86	N 3.47

e) Gadolinium complex of 10-[2-hydroxy-4-oxa-6,6,6-tris(2-oxa-1H,1H,3H,3H,4H,4H-perfluorodecyl)-hexyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

7 g (4.44 mmol) of the title compound from Example 14d) is dissolved in 30 ml of water/50 ml of ethanol/50 ml of chloroform and one adds 0.80 g (2.22 mmol) of gadolinium complex. One stirs for 5 hours at 90°C in an autoclave. The solution is filtered and is evaporated to dryness in a vacuum. /79

Yield: 8.34 g (quantitative) of a colorless, glassy solid.

Water content: 8.1%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 31.94	H 2.74	F 42.83	Gd 9.09	N 3.24
Found:	C 31.74	H 2.91	F 42.67	Gd 8.85	N 3.15

Example 15

a) 1,7-bis[acetyl-(2-(N-ethyl-N-perfluoroctylsulfonylamino]-1,4,7-triazaheptane

20 g (34.17 mmol) of the title compound from Example 1b) and 4.33 g (37.59 mmol) of N-hydroxysuccinimide are dissolved in 150 ml of dimethylformamide. At 0°C, one adds 7.76 g (37.59 mmol) of dicyclohexylcarbodiimide and one stirs for 3 hours at room temperature. One filters off the dicyclohexylurea and one drops the filtrate into a solution consisting of 1.76 g (17.09 mmol) of diethylene triamine and 13.83 g (136.7 mmol) of triethylamine in 200 ml of dimethylformamide at room temperature. One stirs overnight at room temperature. One evaporates to dryness in a vacuum and the residue is absorbed in 200 ml of 5% aqueous soda solution. One extracts twice with 150 ml of dichloromethane each, one dries the combined organic phases over magnesium sulfate and one evaporates to dryness in a vacuum. The residue is chromatographed on silica gel (process agent: dichloromethane/2-propanol = 20/1).

Yield: 16.5 g (78% of theoretical) of a wax-like solid.

Elementary analysis:

Calculated:	C 27.17	H 2.04	F 52.19	N 5.66	S 5.18
Found:	C 27.03	H 2.17	F 52.04	N 5.49	S 5.07

b) 4-(3-carboxy-propanoyl)-1,7-bis-{acetyl-[2-(N-ethyl-N-perfluoroctylsulfonylamino)]}-1,4,7-triazaheptane

To 16 g (12.93 mmol) of the title compound from Example 15a) in 100 ml of methylene chloride, one adds 3.92 g (38.78 mmol) of

triethylamine and one cools the solution down to 0°C. Then one adds 2.59 g (25.86 mmol) of succinic acid anhydride and one stirs for 3 hours at 0°C, overnight at room temperature. One adds 200 ml of 5% hydrochloric acid and one shakes thoroughly. The organic phase is separated and dried over magnesium sulfate. One evaporates to dryness in a vacuum and one chromatographs the residue on silica gel (process agent: dichloromethane/2-propanol = 15/1). /80

Yield: 15.74 g (91% of theoretical) of a colorless solid.

Elementary analysis:

Calculated:	C 28.73	H 2.19	F 48.29	N 5.24	S 4.79
Found:	C 28.58	H 2.40	F 48.17	N 5.17	S 4.65

c) 10-[7-hydroxy-5-aza-4-oxo-octanic acid-N,N-bis(3-aza-4-oxo-6-aza-6-(perfluoroctylsulfonyl)-octyl)-amide]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

15 g (11.21 mmol) of the title compound from Example 15b) and 1.42 g (12.33 mmol) of N-hydroxysuccinimide are dissolved in a mixture of 80 ml of dimethylformamide/30 ml of chloroform. At 0°C, one adds 2.54 g (12.33 mmol) of dicyclohexylcarbodiimide and one stirs for 1 hour at 0° and then for 3 hours at room temperature. One cools down again to 0°C and one adds 4.05 g (40 mol [sic]) of triethylamine/50 ml of 2-propanol. Then one adds 7.07 g (12.33 mmol) of gadolinium complex of 10-[2-hydroxy-3-amino-propyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane dissolved in 30 ml of water and one stirs for 3 hours at room temperature. One evaporates to dryness, one

absorbs the residue in a mixture of 100 ml of methanol/50 ml of chloroform and one filters the dicyclohexylurea off. The filtrate is evaporated to dryness and is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-propanol/acetonitrile).

Yield: 17.76% (78% of theoretical) of a colorless, glassy solid.

Water content: 6.8%.

Elementary analysis (related to anhydrous substance):

Calculated: C 31.08 H 3.03 F 34.12 Gd 8.31 N 7.40 S 3.39

Found: C 30.89 H 3.15 F 34.01 Gd 8.14 N 7.25 S 3.24 /81

Example 16

Gadolinium complex of 1,4,7-tris(carboxylatomethyl)-10-(2-hydroxy-19,19,20,20,21,21,22,22,23,23,24,24,25,25,26,26,26-heptadecafluor-4,7,10,13,16-penta-oxa-hexacosane)-1,4,7,10-tetraazacyclododecane

a) 16,16,17,17,18,18,19,19,20,20,21,21,22,22,22-heptadecafluor-3,6,9,12-tetra-oxa-docosane-1-ol

A mixture of 20 g (32.35 mmol) of 1-p-toluenesulfonyloxy-1H,1H,2H,2H-perfluorodecane [see Example 7a]; 1 g of tetrabutylammonium hydrogen sulfate, 62.83 g (323.5 mmol) of tetraethylene glycol, 300 ml of dichloromethane and 100 ml of 50% caustic soda is stirred intensively for 24 hours at about 5°C. One then dilutes with 200 ml of dichloromethane, one separates the phases and one washes the dichloromethane phase with water. The organic phase is dried over magnesium sulfate and is

evaporated in a vacuum. One gets 18.5 g of the desired title compound as a bright yellow oil.

b) 1,2-epoxy-
19,19,20,20,21,21,22,22,23,23,24,24,25,25,26,26,26-
heptadecafluor-4,7,10,13,16-penta-oxa-hexacosane

A mixture of 17 g (26.5 mmol) of 16,16,17,17,18,18,19,19,20,20,21,21,22,22-heptadecafluor-3,6,9,12-tetra-oxadocosane-1-ol, 0.5 g of tetrabutylammonium hydrogen sulfate, 2.94 g of epichlorhydrin, 200 ml of dichloromethane and 50 ml of 50% caustic soda is stirred intensively for 8 hours at room temperature. One separates the phases, one shakes the aqueous phase with 100 ml of dichloromethane, one combines the organic phases, one shakes with 50 ml of water, one dries over magnesium sulfate and evaporates in a vacuum. The residue is chromatographed on silica gel with hexane/5-50% ethyl acetate and one gets 12.92 g of the title compound in the form of oil.

Elementary analysis: /82

Calculated:	C 36.22	H 3.62	F 46.38
Found:	C 36.00	H 3.78	F 46.20

c) 1,4,7-tris(carboxylatomethyl)-10-(2-hydroxy-
19,19,20,20,21,21,22,22,23,23,24,24,25,25,26,26,26-
heptadecafluor-4,7,10,13,16-penta-oxa-hexacosane)-1,4,7,10-
tetraazacyclododecane

To a solution of 6 g (17.3 mmol) of 1,4,7-(triscarboxylatomethyl) and 4 g of sodium hydroxide in 30 ml of

water, one adds a solution of 12.05 g (17.3 mmol) of 1,2-epoxy-19,19,20,20,21,21,22,22,23,23,24,24,25,25,26,26,26-heptadecafluor-4,7,10,13,16-penta-oxa-hexacosane in 50 ml of tetrahydrofurane. One stirs overnight at 70°C, one evaporates extensively in a vacuum, one absorbs the residue in 150 ml of water, one adjusts a pH of 3 with 6N hydrochloric acid, and one extracts several times with n-butanol. The combined extracts are evaporated in a vacuum and the residue is purified by means of chromatography on RP-18 with a gradient consisting of water/n-butanol/acetonitrile. One gets 13.71 g of the title compound in the form of a yellow viscous oil.

Elementary analysis:

Calculated:	C 40.31	H 4.93	F 30.97	N 5.37
Found:	C 40.08	H 5.21	F 30.77	N 5.29

d) Gadolinium complex of 1,4,7-tris(carboxylatomethyl)-10-(2-hydroxy-19,19,20,20,21,21,22,22,23,23,24,24,25,25,26,26,26-heptadecafluor-4,7,10,13,16-penta-oxa-hexacosane)-1,4,7,10-tetraazacyclododecane

One mixes a mixture consisting of 5 g (4.79 mmol) of 1,4,7-tris(carboxylatomethyl)-10-(2-hydroxy-19,19,20,20,21,21,22,22,23,23,24,24,25,25,26,26,26-heptadecafluor-4,7,10,13,16-penta-oxa-hexacosane)-1,4,7,10-tetraazacyclododecane in 50 ml of water and 30 ml of ethanol with 869 mg (2.397 mmol) of gadolinium oxide and one heats for 5 hours under reflux. One filters the hot solution and one evaporates in

a vacuum. One gets 5.60 g of the title compound in the form of a glassy solid substance with a water content of 4.1%. /83

Elementary analysis (related to anhydrous substance):

Calculated:	C 35.12	H 4.04	F 26.98	Gd 13.14	N 4.68
Found:	C 34.90	H 4.38	F 26.70	Gd 13.10	N 4.62

Example 17

Gadolinium complex of 1,4,7-tris(carboxylatomethyl)-10-(4-aza-2-hydroxy-26,26,26,25,25,24,24,23,23,22,22,21,21,20,20,19,19-heptadecafluor-5-oxo-16-thia-hexacosyl)-1,4,7,10-tetraazacyclododecane

a) 22,22,22,21,21,20,20,19,19,18,18,17,17,16,16,15,15-heptadecafluor-12-thia-docosanoic acid

One mixes a solution of 10 g (37.71 mmol) of 11-bromoundecanic acid in 150 ml of dichloromethane with 11.43 g of triethylamine and 18.11 g (37.71 mmol) of 1H,1H,2H,2H-perfluorodecyl mercaptan and one stirs overnight at room temperature. One extracts the solution several times with 2N of hydrochloric acid, one washes with common salt solution, one dries over magnesium sulfate and one evaporates in a vacuum. One gets 21.5 g of the title compound in the form of a yellow oil.

Elementary analysis:

Calculated:	C 37.96	H 3.79	F 48.61	S 4.83
Found:	C 38.30	H 4.01	F 48.40	S 5.20

b) Gadolinium complex of 1,4,7-tris(carboxylatomethyl)-10-(4-aza-2-hydroxy-26,26,26,25,25,24,24,23,23,22,22,21,21,20,20,19,19-

heptadecafluor-5-oxo-16-thia-hexacosyl)-1,4,7,10-tetraazacyclododecane /84

5 g (7.52 mmol) of the title compound from Example 17a) and 0.95 g of N-hydroxysuccinimide are dissolved in a mixture of 25 ml of dimethylformamide and 15 ml of chloroform. At 0°C, one adds 1.71 g of dicyclohexylcarbodiimide and one stirs for 1 hour at 0°C and then for 3 hours at room temperature. One then cools down again to 0°C and one mixes with 3 ml of triethylamine and 20 ml of n-propanol. Subsequently, one adds 4.75 g (82.7 mmol) of the gadolinium complex of 10-(3-amino-2-hydroxy-propyl)-1,4,7-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecane dissolved in 25 ml of water and one stirs for 3 hours at 20°C. One evaporates to dryness, one absorbs the residue in a mixture consisting of 55 ml of methanol and 20 ml of chloroform and one filters off the dicyclohexylurea. The filtrate is evaporated to dryness and it is purified by means of chromatography on RP-18 with a gradient from of water/n-propanol/acetonitrile. One gets 6.15 g of the title compound in the form of a glassy solid. with a water content of 2.3%.

Elementary analysis (related to anhydrous substance):

Calculated: C 37.41 H 4.38 F 26.47 Gd 12.89 N 5.74 S 2.63

Found: C 37.08 H 4.60 F 26.30 Gd 12.68 N 5.91 S 2.49

Example 18

Gadolinium complex of 1,4,7-tris(carboxylatomethyl)-10-[1-(1,2-dihydroxyethyl)-3-oxa-6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluor]undecane-1,4,7,10-tetraazacyclododecane

a) 1-p-toluenesulfonyloxy-1H,1H,2H,2H-perfluoroctane

To a solution of 25 g (68.7 mmol) of 1H,1H,2H,2H-perfluoroctane-1-ol in 300 ml of dichloromethane, one adds at 0°C 20 ml of pyridine and, while stirring, one introduces in portions 13.49 g (70.76 mmol) of p-toluene sulfonic chloride. One stirs for another 3 hours at 0°C, one extracts the dichloromethane in a vacuum at room temperature.

The remaining pyridine solution is now mixed with ice water and the desired product is precipitated. One decants and one dissolves the residue in dichloromethane, one washes the solution with water, one dries over magnesium sulfate and one evaporates in a vacuum. The residue is purified by means of chromatography on silica gel with hexane/5-40% ethyl acetate. One gets 29.2 g of the title compound in the form of a viscous foam. /85

Elementary analysis:

Calculated:	C 34.76	H 2.14	F 47.65	S 6.19
Found:	C 34.98	H 2.38	F 47.39	S 6.42

b) 1,4,7-tris(benzyloxycarbonyl)-10-[1-(2,2-dimethyl-1,3-dioxolane-4-yl)-6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluor-3-oxa]-undecane-1,4,7,10-tetraazacyclododecane

To 7.33 g (10 mmol) of 1,4,7-tris(benzyloxycarbonyl)-10-[2-hydroxy-1-(2,2-dimethyl-1,3,-dioxolane-4-yl)]-ethyl-1,4,7,10-tetraazacyclododecane [J. Mag. Res. Imag. 5: 7-10, (1955)] dissolved in 100 ml of dichloromethane, one adds in succession 20 ml of 50% caustic soda, 0.5 g tetrabutylammonium hydrogen sulfate and 5.18 g (10 mmol) of 1-p-toluenesulfonyloxy-1H,1H,2H,2H-

perfluoroctane [see Example 18a] and stirs the mixture intensively overnight at room temperature. One separates the phases, one washes the organic phase several times with water, one dries over magnesium sulfate and one evaporates in a vacuum. The residue is purified by means of chromatography on silica gel with dichloromethane/1-10% ethanol. One gets 8.02 g of the title compound in the form of a viscous oil.

Elementary analysis:

Calculated:	C 53.01	H 5.02	F 23.19	N 5.26
Found:	C 53.30	H 5.39	F 23.01	N 5.40

c) 1-[1-(2,2-dimethyl-1,3-dioxolane-4-yl)-6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluor-3-oxa]-undecane-1,4,7,10-tetraazacyclododecane /86

A solution of 7 g (6.57 mmol) of 1,4,7-tris(benzyloxycarbonyl)-10-[1-(2,2-dimethyl-1,3-dioxolane-4-yl)-6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluor-3-oxa]-undecane-1,4,7,10-tetraazacyclododecane in 100 ml of isopropyl alcohol is mixed with 0.7 g of palladium on carbon (10%) and is shaken for 3 hours in a hydrogen atmosphere. One filters off the catalyst and one evaporates the solution in a vacuum. On gets 4.20 g of the title compound in the form of a glassy foam.

Elementary analysis:

Calculated:	C 41.70	H 5.32	F 37.28	N 8.46
Found:	C 41.61	H 5.57	F 37.10	N 8.59

d) 1,4,7-tris(carboxylatomethyl)-10-[1-(1,2-dihydroxy-ethyl)-3-oxa-6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluor]undecane-1,4,7,10-tetraazacyclododecane

One dissolves 3.36 g (24.15 mmol) of bromoacetic acid in 50 ml of water and one mixes with 6N caustic soda up to a pH of 7. At 40°C, while stirring, one simultaneously drops in a solution of 4 g (6.04 mmol) of 1-[1-(2,2-dimethyl-1,3-dioxolane-4-yl)-6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluor-3-oxa]-undecane-1,4,7,10-tetraazacyclododecane dissolved in 20 ml of isopropyl alcohol and one adds so much 6N caustic soda that the pH is kept at 9-10. Then one mixes with semi-concentrated hydrochloric acid up to a pH of 1 and one continues to stir another 3 hours at 60°C. One cools down to room temperature and one extracts the solution several times with n-butanol. The organic extract is evaporated and the residue is purified by means of chromatography on RP-18 with a gradient from water/n-butanol/acetonitrile. One gets 3.85 g of the title compound in the form of a yellow oil with a water content of 3.9%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 39.20	H 4.68	F 31.00	N 7.03
Found:	C 39.08	H 4.98	F 30.72	N 7.29

e) Gadolinium complex of 1,4,7-tris(carboxylatomethyl)-10-[1-(1,2-dihydroxy-ethyl)-3-oxa-6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluor]undecane-1,4,7,10-tetraazacyclododecane /87

One mixes a mixture consisting of 1.59 g (2 mmol) of 1,4,7-tris(carboxylatomethyl)-10-[1-(1,2-dihydroxy-ethyl)-3-oxa-

6,6,7,7,8,8,9,9,10,10,11,11,11-tridecafluor]undecane-1,4,7,10-tetraazacyclododecane, 25 ml of water and 15 ml of ethanol with 363 mg (1 mmol) of gadolinium oxide and one heats for 5 hours under reflux. One filters the hot solution, one evaporates in a vacuum and one gets 1.85 g of the title compound in the form of a glassy solid substance with a water content of 4.2%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 32.84	H 3.60	F 25.98	Gd 16.54	N 5.89
Found:	C 32.53	H 3.71	F 25.72	Gd 16.39	N 5.93

Example 19

Gadolinium complex of 1,4,7-tris(carboxylatomethyl)-10-{2-hydroxy-4-oxa-4-[4-2H,2H,3H,3H-1-oxa-perfluorundec-1-yl]-phenyl)-but-1-yl-1,4,7,10-tetraazacyclododecane

a) 1-hydroxy-4-(2H,2H,3H,3H-1-oxa-perfluorundec-1-yl)-benzene

5 g (45.41 mmol) of hydroquinone are mixed with 100 ml of acetone and while stirring in succession, are mixed with 13.8 g potassium carbonate and 14.04 g (22.7 mmol) of 1-p-toluene sulfonyloxy-1H,1H,2H,2H-perfluorodecane [see Example 7a)]. One heats for 6 hours under reflux, one then concentrates extensively in a vacuum, one dilutes with 200 ml of water, one sets a pH of 3 with citric acid and one extracts several times with dichloromethane. The organic extract is dried over magnesium sulfate and is evaporated in a vacuum. The residue is purified by means of chromatography on silica gel with hexane/5-30% ethyl acetate. One gets 8.20 g of the desired title compound in the form of a viscous oil.

Elementary analysis: /88

Calculated:	C 34.55	H 1.63	F 58.07
Found:	C 34.31	H 1.79	F 58.01

b) 1-(3,4-epoxy-1-oxa-but-1-yl)-4-(2H,2H,3H,3H-1-oxa-perfluorundec-1-yl)-benzene

A mixture consisting of 8 g (14.38 mmol) of 1-hydroxy-4-(2H,2H,3H,3H-1-oxa-perfluorundecyl-1-yl)-benzene, 0.4 g of tetrabutylammonium hydrogen sulfate, 1.60 g (17.26 mmol) of epichlorhydrin, 150 ml of dichloromethane and 30 ml of 50% caustic soda is stirred intensively for 30 minutes in an ice bath and then for 5 hours at room temperature. One separates the phases, one washes the organic phase with water, one dries over magnesium sulfate and one evaporates in a vacuum. The residue is purified by means of chromatography on silica gel with hexane/5-30% ethyl acetate and one gets 6.60 g of the desired title compound in the form of a viscous oil.

Elementary analysis:

Calculated:	C 37.27	H 2.41	F 52.75
Found:	C 37.10	H 2.66	F 52.80

c) 1,4,7-tris(carboxylatomethyl)-10-{2-hydroxy-4-oxa-4-[4-2H,2H,3H,3H-1-oxa-perfluorundec-1-yl)]-phenyl}-but-1-yl-1,4,7,10-tetraazacyclododecane

To a solution of 3.46 g (10 mmol) of 1,4,7-tris(carboxylatomethyl)-1,4,7,10-tetraazacyclododecane and 2.5 g of sodium hydroxide in 25 ml of water, one adds a solution of 6.12 g (10 mmol) of 1-(3,4-epoxy-1-oxa-but-1-yl)-4-(2H,2H,3H,3H-

1-oxa-perfluorundec-1-yl)-benzene in 25 ml of tetrahydrofurane and one heats for 24 hours under reflux, one then extensively evaporates in a vacuum, one dissolves the residue in 100 ml of water, one adjusts a pH of 3 with the help of 6N hydrochloric acid and one extracts several time with n-butanol. The combined extracts are evaporated in a vacuum. The residue is purified by means of chromatography on RP-18 with a gradient from water/n-butanol/acetonitrile. One gets 6.71 g of the title compound in the form of a viscous oil. /89

Elementary analysis:

Calculated:	C 41.35	H 4.10	F 33.69	N 5.84	
Found:	C 41.58	H 4.38	F 33.50	N 5.91	

d) Gadolinium complex of 1,4,7-tris(carboxylatomethyl)-10-{2-hydroxy-4-oxa-4-[4-(2H,2H,3H,3H-1-oxa-perfluorundec-1-yl)]-phenyl}-but-1-yl-1,4,7,10-tetraazacyclododecane

One mixes a mixture of 4.79 g (5 mmol) of 1,4,7-tris(carboxylatomethyl)-10-{2-hydroxy-4-oxa-4-[4-(2H,2H,3H,3H-1-oxa-perfluorundec-1-yl)]-phenyl}-but-1-yl-1,4,7,10-tetraazacyclododecane, 50 ml of water and 30 ml of ethanol with 906 mg (2.5 mmol) of gadolinium complex and one heats for 5 hours under reflux. One filters the hot solution and one evaporates in a vacuum. One gets 5.50 g of the title compound in the form of a glassy solid substance with a water content of 4.9%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 35.62	H 3.26	F 29.02	Gd 14.13	N 5.03
Found:	C 35.40	H 3.50	F 28.81	Gd 14.01	N 5.18

Example 20

Gadolinium complex, disodium salt of 3,9-bis(carboxymethyl)-6-[(1-carboxy)-1H,2H,2H,4H,4H,5H,5H-3-oxa-perfluortridecyl]-3,6,9-triazaundecanic diacid

a) N-t-butoxycarbonyl-serine-(1H,1H,2H,2H-perfluordecyl)-ether-benzyl ester

Into a solution of 2.953 g (10 mmol) of N-t-butyloxycarbonyl-serine benzyl ester (brand name Bachem) in 30 ml of dry dimethylformamide, one adds in portions 300 mg (10 mmol) of sodium hydride (80% in oil). After dissolution, one mixes with 6.072 (10 mmol) of the tosylate made under 7a). One stirs for 12 hours at room temperature. Then one pours in 500 ml of ice water, one absorbs the product in dichloromethane, one washes the organic solution with water, one dries over sodium sulfate and one concentrates to dryness. The residue is purified by means of chromatography on silica gel. As eluent, one uses a mixture of dichloromethane with increasing methanol addition. /90

The title compound is obtained in the form of a syrup.

Yield: 5.902 g (79.6% of theoretical).

Elementary analysis:

Calculated:	C 40.50	H 3.26	F 43.56	N 1.89
Found:	C 40.64	H 3.37	F 43.49	N 1.83

b) Serine-(1H,1H,2H,2H-perfluordecyl)-ether-benzyl ester (as salt of trifluoracetic acid)

In 50 ml of a mixture consisting of trifluoracetic acid and dichloromethane in a ratio of 2:1, one dissolves 7.414 g (10

mmol) of the N-protected compound produced under 20a) and one stirs overnight at room temperature. One concentrates to dryness and one removes residues of trifluoracetic acid by codistillation with ethanol. The title compound is obtained in the form of a salt of trifluoracetic acid.

Yield: 7.418 g (98.2% of theoretical)

Elementary analysis:

Calculated:	C 34.98	H 2.27	F 50.30	N 1.85
Found:	C 34.89	H 2.31	F 50.39	N 1.80

c) 3,9-bis(t-butoxycarbonylmethyl)-6-[(1-benzyloxycarbonyl)-1H,2H,2H,4H,4H,5H,5H-3-oxa-perfluorotridecyl)-3,6,9-triazaundecanic-diacid-di(t-butyl)-ester

Into a mixture of 10 ml of acetonitrile and 20 ml of phosphate buffer with a pH value of 8.0, one places 3.777 g (5 mmol) of the amine-trifluoracetate made under 20b) and 3.523 g (10 mmol) of N,N-bis(t-butyloxycarbonylmethyl)-2-(bromethyl)-amine and one stirs intensively at room temperature. Then one separates the buffer phase, one extracts with 10 ml of acetonitrile and one adds it to the organic phase. After adding 20 ml of fresh buffer, one stirs for another 20 hours at room temperature. One separates the organic phase, one concentrates it and one distributes the residue between 100 ml of phosphate buffer (pH 8.0) and 100 ml of acetic ether. The organic phase is washed with saturated common salt solution, it is dried over sodium sulfate and it is concentrated. The title compound is purified by means of chromatography on silica gel.

Dichloromethane with a rising addition of methanol is used as eluent. The title compound is obtained in the form of a glassy solid. /91

Yield: 3.162 (53.4% of theoretical)

Elementary analysis:

Calculated:	C 48.69	H 5.62	F 27.28	N 3.55
Found:	C 48.82	H 5.72	F 27.37	N 3.50

d) 3,9-bis(carboxymethyl)-6-[(1-carboxyl)-1H,2H,2H,4H,4H,5H,5H-3-oxa-perfluor-tridecyl)-3,6,9-triazaundecanic-diacid

Into a mixture of 25 ml of trifluoracetic acid/dichloromethane in ratio of 2:1, one puts 5.920 g (5 mmol) of the compound made under 20c). One stirs overnight at room temperature, one then concentrates to dryness, one absorbs the residue in 100 ml of 3N hydrochloric acid, one heats for 3 hours under reflux, one then concentrates in a vacuum to dryness and one absorbs in 160 ml of a mixture consisting of water, ethanol and chloroform (10:5:1). The solution is set at a constant pH value (about 3) by adding ion exchanger IRA 67 (OH^- form). One suctions off quickly, one concentrates and one gets the title compound in the form of a glassy solid.

Yield: 3.080 g (71.3% of theoretical)

Water content: 11.3%

Elementary analysis (related to anhydrous substance):

Calculated:	C 34.53	H 3.25	F 37.15	N 4.83
Found:	C 34.41	H 3.32	F 37.29	N 4.90

e) Gadolinium complex, disodium salt of 3,9-bis(carboxymethyl)-6-[(1-carboxy)-1H,2H,2H,4H,4H,5H,5H-3-oxa-perfluorotridecyl]-3,6,9-triazaundecanic diacid /92

Into a mixture consisting of 60 ml of distilled water and 30 ml of ethanol, one puts 2.941 g (3.0 mmol calculated for 11.3% water content) of the acid made under 20d). While stirring and heating to 50°C, one adds in portions 54.38 mg (1.5 mmol) of gadolinium oxide. After the addition has been completed, one stirs up to solution. One then sets the pH value of the solution at 7.2 by adding caustic soda. The solution is then concentrated in connection with which one can observe intensive foaming. The residue is codistilled with distilled water. The title compound is obtained as a glassy solid.

Yield: 3.489 g (quantitative).

Water content: 8.2%.

Elementary analysis (related to anhydrous substance):

Calculated: C 38.12 H 2.17 F 30.25 Gd 14.73 N 3.94 Na 4.31

Found: C 28.25 H 2.26 F 30.40 Gd 14.85 N 3.99 Na 4.38

Example 21

Gadolinium complex, monosodium salt of 3,6,9-tris(carboxymethyl)-3,6,9-triazaundecanic-diacid-mono-N-{ethyl-2-amino-[carbonylmethyl-amino-(N-ethyl-N-perfluoroctylsulfonyl)]}-amide

a) 3,6,9-tris(carboxylatomethyl)-3,6,9-triazaundecanic-diacid-mono-N-{ethyl-2-amino-[carbonylmethyl-amino-[N-ethyl-N-perfluoroctylsulfonyl)]}-amide

In 200 ml of a mixture consisting of dimethylformamide and dichloromethane in a ratio of 4:1, one suspends 17.87 g (50 mmol) of diethylene triamine pentacetic acid bisanhydride, and in portions while stirring forcefully, one mixes with the mixture of 3.137 g (5 mmol) of [N-(2-aminoethyl)-N-perfluoroctylsulfonyl]-aminoacetic-acid-N-(2-aminoethyl)-amide and 6.50 g (64.2 mmol) of triethylamine. One continues stirring for 5 hours, one concentrates to dryness, one mixes with 300 ml of ice water and one sets the pH value of the preparation at about 3 with the help of 3N hydrochloric acid. One extracts twice with 200 ml of n-butanol each, one combines the organic solutions and one concentrates them. The product is purified by means of chromatography on silica gel RP-18. Water and tetrahydrofurane are used as eluent. The title compound is obtained in the form of a glassy solid. /93

Yield: 2.722 g (54.3% of theoretical).

Water content: 9.7%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 33.54	H 3.52	F 32.21	N 8.38	S 3.20
Found:	C 33.65	H 3.60	F 32.14	N 8.51	S 3.29

b) Gadolinium complex, monosodium salt of 3,6,9-tris(carboxymethyl)-3,6,9-triazaundecanic-diacid-mono-N-{ethyl-2-amino-[carbonylmethyl-amino-(N-ethyl-N-perfluoroctylsulfonyl)]}-amide

In 90 ml of a mixture of distilled water and ethanol (2:1), one puts 3.259 g (3 mmol calculated for 9.7% water) of the

compound made under 21a). One adds 543.8 mg (1.5 mmol) of gadolinium oxide in portions while stirring. One stirs up to solution, one then sets the pH value at 7.2 by adding caustic soda, one concentrates, which is accompanied by intensive foaming. The residue is codistilled with distilled water. The title compound is obtained in the form of a glassy solid.

Yield: 3.861 g (quantitative).

Water content: 8.4%.

The elementary analysis is calculated for anhydrous substance.

Calc.: C 28.53 H 2.65 F 27.40 Gd 13.34 N 7.13 Na 1.95 S 2.72

Found: C 28.61 H 2.68 F 27.48 Gd 13.40 N 7.08 Na 1.99 S 2.76

Example 22

Gadolinium complex, monosodium salt of 3,9-bis(carboxymethyl)-6-1H,1H,4H,4H,5H,5H,8H,8H,10H,10H,11H,11H-2,7-dioxo-3,6-diaza-9-oxa-perfluoromonodecyl)-3,6,9-triazaundecanic-diacid /94

a) Glycolic acid-(1H,1H,2H,2H-perfluorodecyl)-ether-N-(2-aminoethyl)-amide

10.44 g (20 mmol) of the compound in 2b) are dissolved in 80 ml of dichloromethane and are mixed with 2.30 g (20 mmol) of N-hydroxysuccinimide as well as 4.13 g (20 mmol) of dicyclohexylcarbodiimide. One continues to stir overnight, one filters off the dicyclohexylurea and one stirs the filtrate into a solution of 60.1 g (1,000 mmol) of ethylenediamine in 100 ml of dichloromethane. One continues to stir overnight, one mixes with 1.5 l of water and one separates the organic phase. One washes

the dichloromethane solution with water, one dries over sodium sulfate, one concentrates to dryness and one purifies the residue by means of chromatography on silica gel. A mixture of dichloromethane with an increasing addition of isopropanol is used as eluent.

Yield: 9.615 g (85.2% of theoretical).

Elementary analysis:

Calculated:	C 29.80	H 2.32	F 57.24	N 4.96
Found:	C 29.96	H 2.37	F 57.12	N 5.01

b) Glycolic acid-(1H,1H,2H,2H-perfluorodecyl)-ether-N-(ethyl-2-(benzyloxycarbonylaminomethylcarbonylamino)]-amide

2.092 g (10 mmol) of benzyloxycarbonylglycine is dissolved in 15 ml of dichloromethane and are mixed with 1.151 g (10 mmol) N-hydroxysuccinimide as well as 2.063 g (10 mmol) of dicyclohexylcarbodiimide. One continues to stir overnight, one filters off the dicyclohexylurea and one concentrates to dryness. The residue is purified on silica gel by means of column chromatography. A mixture of dichloromethane and ethanol is used as eluent. The title compound is contained in the form of a glassy solid.

Yield: 6.905 g (91.4% of theoretical).

Elementary analysis: /95

Calculated:	C 38.16	H 2.94	F 42.75	N 5.56
Found:	C 38.28	H 2.98	F 42.82	N 5.50

c) Glycolic acid-(1H,1H,2H,2H-perfluorodecyl)-ether-N-(ethyl-2-aminomethylcarboxylamino)]-amide

In 100 ml of a mixture consisting of tetrahydrofurane and ethanol in a ratio of 2:1, one hydrates 3.777 g (5 mmol) of the compound made under 22b) in the presence of 0.2 g Pearlman catalyst (Pd 20%/C) up to the absorption of 112 ml of hydrogen. One suctions off the catalyst, one washes thoroughly with ethanol and one concentrates to dryness. The title compound is obtained in the form of a glassy solid.

Yield: 3.097 g (99.7% of theoretical).

Elementary analysis:

Calculated:	C 30.93	H 2.60	F 51.98	N 6.76
Found:	C 30.87	H 2.64	F 52.11	N 6.82

d) 3,9-bis(t-butyloxycarbonylmethyl)-6-(1H,1H,4H,4H,5H,5H,8H,8H,10H,10H,11H,11H-2,7-dioxo-3,6-diaza-9-oxa-perfluorononadecyl)-3,6,9-triazaundecane-diacid-bis(t-butyl ester)

Into a mixture consisting of 10 ml of acetonitrile and 20 ml of phosphate buffer with a pH value 8, one puts 3.107 g (5 mmol) of the amine made under 22c) and 3.525 g (10 mmol) N,N-bis(t-butyloxycarbonylmethyl)-2-(bromethyl)-amine and one stirs intensively for 2 hours at room temperature. Then one separates the buffer phase, one extracts with 10 ml of acetonitrile and one adds it to the organic phase. After adding 20 ml of fresh buffer, one stirs for another 20 hours at room temperature. One separates the organic phase, one concentrates it and one distributes the residue between 100 ml of phosphate buffer (pH 8.0) and 100 ml of acetic ether. The organic phase is washed

with saturated common salt solution, it is dried over sodium sulfate and concentrated. The compound is purified by means of chromatography on silica gel. Dichloromethane with a growing addition of methanol is used as eluent. The title compound is obtained in the form of a glassy solid. /96

Yield: 3.044 g (52.3% of theoretical).

Elementary analysis:

Calculated:	C 45.40	H 5.71	F 27.75	N 6.02
Found:	C 45.47	H 5.78	F 27.68	N 6.10

e) 3,9-bis(t-carboxymethyl)-6-(1H,1H,4H,4H,5H,5H,8H,8H,10H,10H,11H,11H-2,7-dioxo-3,6-diaza-9-oxa-perfluorononadecyl)-3,6,9-triazaundecane-diacid

Into a mixture of 120 ml of trifluoracetic acid/dichloromethane in a ratio of 2:1, one puts 5.820 g (5 mmol) of the compound made under 22d). One continues to stir overnight at room temperature, one concentrates to dryness, one removes the residues of trifluoracetic acid by codistillation with ethanol and one absorbs in 240 ml of a mixture consisting of water, ethanol and chloroform. The solution is set at a constant pH value (about 3) by adding ion exchanger IRA-67 (OH^- form). One suctions off quickly, one concentrates and one gets the title compound in the form of a glassy solid.

Yield: 3.214 g (68.4% of theoretical).

Water content: 10.3%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 35.79	H 3.65	F 34.37	N 7.45

Found: C 35.90 H 3.72 F 34.31 N 7.51

f) Gadolinium complex, monosodium salt of 3,9-bis(carboxymethyl)-6-(1H,1H,4H,4H,5H,5H,8H,8H,10H,10H,11H,11H-2,7-dioxo-3,6-diaza-9-oxa-perfluorononadecyl)-3,6,9-triaza-undecanic diacid /97

Into a mixture consisting of 60 ml of distilled water and 30 ml of ethanol, one adds 3.143 g (3.0 mmol calculated for 10.3% water content) of the acid made under 22e). While stirring and heating to 50°C, one adds 543.8 mg (1.5 mmol) of gadolinium oxide in portions. After the addition has been completed, one stirs until solution. One then sets the pH value of the solution at 7.2 by adding caustic soda, one concentrates the solution in connection with which one can observe intensive foaming. The residue is codistilled with distilled water. The title compound is obtained in the form of a glassy solid.

Yield: 3.635 g (quantitative).

Water content: 7.9%.

Elementary analysis (related to anhydrous substance):

Calculated: C 30.14 H 2.71 F 28.95 Gd 14.09 N 6.28 Na 2.06

Found: C 30.21 H 2.28 F 29.03 Gd 14.16 N 6.22 Na 2.11

Example 23

Gadolinium complex of 3,6,9-tris(carboxymethyl)-3,6,9-triazaundecanic-diacid-bis{N-[2-aminoethyl-(N-ethyl-N-perfluoroctylsulfonyl]-amide

a) N-ethyl-(2-benzyloxycarbonylamino-ethyl)-perfluoroctylsulfonic acid amide

5.272 g (10 mmol) of perfluoroctylsulfonic acid-N-ethylamide are dissolved in 30 ml of dimethylformamide. Excluding moisture, one mixes with 330 mg (11 mmol) of sodium hydride (80% in oil). After the end of gas generation, one drips in the solution of 2.093 g (10 mmol) of N-benzoyloxycarbonyl aziridine. One pours in 300 ml of ice water, one extracts with dichloromethane, one washes the organic solution with water, one dries it over sodium sulfate and one concentrates to dryness. The residue is chromatographed on silica gel with dichloromethane/methanol. The title compound is a glass-like solid. /98

Yield: 6.149 (87.3% of theoretical).

Elementary analysis:

Calculated:	C 34.10	H 2.43	F 45.85	N 3.98	S 4.55
Found:	C 34.00	H 2.49	F 45.97	N 4.06	S 4.49

b) N-ethyl-N-2-(aminoethyl)-perfluoroctylsulfonamide

In 100 ml of a mixture of tetrahydrofurane and ethanol in a ratio of 2:1, one hydrates 3.522 g (5 mmol) of the compound made under 23a) in the presence of 0.2 g Pearlman catalyst (Pd 20%/C) up to the absorption of 112 ml of hydrogen. One suctions off the catalyst, one washes thoroughly with ethanol and one concentrates to dryness. The title compound is obtained in the form of an amorphous solid.

Yield: 2.814 g (98.7% of theoretical).

Elementary analysis:

Calculated:	C 25.97	H 1.94	F 56.64	N 4.91	S 5.62
Found:	C 25.39	H 1.99	F 56.57	N 4.96	S 5.53

c) 3,6,9-tris(carboxymethyl)-3,6,9-triazaundecanic-diacid-bis{N-[2-aminoethyl-(N-ethyl-N-perfluoroctylsulfonyl)]-amide}

5.703 g (10 mmol) of the compound made under 23b) as well as 1.518 g (15 mmol) of triethylamine are dissolved in 30 ml of dry dimethylformamide and are mixed in portions while stirring and with the exclusion of moisture with 1.787 g (5 mmol) of diethylene triaminepenta-acetic acid-bisanhydride. One continues stirring overnight, one then concentrates, one mixes with water, one sets the pH value at about 3 with the help of 3N hydrochloric acid and one extracts twice with 100 ml of n-butanol each. The organic solutions are combined, concentrated and are subjected to chromatography on silica gel RP-18. Water and tetrahydrofurane are used as eluent. The title compound is obtained in the form of a glass-like solid.

Yield: 6.172 g (82.4% of theoretical). /99

Water content: 9.8%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 30.47	H 2.76	F 43.12	N 6.55	S 4.28
Found:	C 30.59	H 2.81	F 43.00	N 6.61	S 4.33

d) Gadolinium complex of 3,6,9-tris(carboxymethyl)-3,6,9-triazaundecanic-diacid-bis{N-[2-aminoethyl-(N-ethyl-N-perfluoroctylsulfonyl]-amide

Into a mixture of 120 ml of distilled water, 60 ml of ethanol and 20 ml of chloroform, one adds 6.570 g (4 mmol calculated on the basis of 9.8% water content) of the compound made under 23c). While stirring and heating to 50°C, one adds 725 mg (82.0 mmol) of gadolinium oxide in portions. One stirs until solution, one then concentrates in connection with which one can observe intensive foaming and one subjects the residue to codistillation with distilled water. Codistillation is repeated twice. The title compound is obtained in the form of a glass-like solid.

Yield: 7.191 g (quantitative).

Water content: 8.1%.

Elementary analysis (related to anhydrous substance):

Calculated: C 27.63 H 2.32 F 39.10 Gd 9.52 N 5.93 S 3.88

Found: C 27.50 H 2.37 F 39.22 Gd 9.61 N 5.85 S 3.95

Example 24

Gadolinium complex of 3,6,9-tris(carboxymethyl)-3,6,9-triazaundecanic-diacid-bis{N-<2-aminoethyl-[glycolic acid-(1H,1H,2H,2H-perfluorodecyl-ether)-amide]>-amide}

a) 3,6,9-tris(carboxymethyl)-3,6,9-triazaundecanic-diacid-bis{N-<2-aminoethyl-glycolic acid-(1H,1H,2H,2H-perfluorodecyl-ether)-amide]>-amide}

6.771 g (12 mmol) of the compound made according to Example 22a) as well as 1.821 g (18 mmol) of triethylamine are dissolved in 40 ml of dry dimethylformamide and are mixed in portions while stirring and with the exclusion of moisture with 2.144 g (6 mmol)

diethyltriamine-pentacetic acid bisanhydride. One stirs overnight, whereupon one concentrates, mixes with 20 ml of water, sets the pH value at about 3 and extracts with 3N hydrochloric acid twice with 150 ml of butanol each. The organic solutions are combined, concentrated, and one subjects the residue to chromatography on RP-18 silica gel. Water and tetrahydrofurane are used as eluent. The title compound is obtained in the form of a glass-like solid. /100

Yield: 6.989 g (78.4% of theoretical).

Water content: 7.1%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 33.95	H 3.05	F 43.47	N 6.60
Found:	C 34.06	H 3.11	F 43.40	N 6.67

b) Gadolinium complex of 3,6,9-tris(carboxymethyl)-3,6,9-triazaundecanic-diacid-bis{N-<2-aminoethyl-[glycolic acid-(1H,1H,2H,2H-perfluorodecyl-ether)-amide]>-amide}

Into a mixture of 100 ml of distilled water, 50 ml of ethanol and 20 ml of chloroform, one adds 4.798 g (3 mmol calculated on the basis of 7.1% water content) of the compound made under 24a). While stirring and heating to 50°C, one adds 543.8 mg (1.5 mmol) of gadolinium oxide in portions. One stirs until solution, one then concentrates in connection with which one can observe intensive foaming. The residue is codistilled several times with distilled water. The title compound is obtained in the form of a glass-like solid.

Yield: 5.285 g (quantitative).

Water content: 6.9%.

The elementary analysis is calculated for anhydrous substance.

Calculated:	C 30.76	H 2.58	F 39.39	Gd 9.59	N 5.98
Found:	C 30.87	H 2.65	F 39.51	Gd 9.69	N 6.11

Example 25 /101

Gadolinium complex, sodium salt of 3,9-bis(carboxymethyl)-6-[N-1H,1H,2H,2H-perfluorodecyl)-aminocarbonylmethyl-3,6,9-triazaundecanic-diacid

a) N-benzyloxycarbonylglycine-N-(1H,1H,2H,2H-perfluorodecyl)-amide

In 70 ml of dichloromethane, one dissolves 7.877 g (15 mmol) of 1H,1H,2H,2H-perfluorodecylamine (J. Fluor. Chem. 55, 85 (1991)) and are mixed with 1.726 g (15 mmol) of N-hydroxysuccinimide, 3.095 g (15 mmol) of dicyclohexylcarbodiimide and 3.138 g (15 mmol) of N-benzyloxycarbonylglycine (brand name Bachem). One stirs overnight, one filters the dicyclohexylurea off, one concentrates and subjects the residue to column chromatography on silica gel. Mixtures consisting of dichloromethane and ethanol are used as eluent. The title compound is obtained in the form of a solid.

Yield: 8.951 g (91.2% of theoretical).

Elementary analysis:

Calculated:	C 36.71	H 2.31	F 49.36	N 4.28
Found:	C 36.87	H 2.39	F 49.51	N 4.37

b) Glycine-N-(1H,1H,2H,2H-perfluorodecyl)-amide

7.594 g (10 mmol) of the compound made according to 28a) are dissolved in 150 ml of a mixture consisting of tetrahydrofurane and ethanol in a ratio of 2:1 and are hydrated in the presence of 0.25 g Pearlman catalyst (Pd 20%/C) up to the absorption of 224 ml of hydrogen. One suctions off the catalyst, washes thoroughly with ethanol and concentrates up to dryness. The title compound is obtained in the form of an amorphous solid.

Yield: 6.21 g (99.3% of theoretical).

Elementary analysis:

Calculated:	C 25.37	H 1.60	F 56.84	N 4.93
Found:	C 25.28	H 1.65	F 56.92	N 4.99

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c) 3,9-bis(t-butyloxycarbonylmethyl)-6-N-(1H,1H,2H,2H-perfluorodecyl)-aminocarbonylmethyl-3,6,9-triazaundecanic-diacid-di(t-butylester)

Into a mixture of 10 ml of acetonitrile and 20 ml phosphate buffer with a pH value of 8.0, one adds 2.841 g (5 mmol) of the amine made according to 25b) and 3.875 g (11 mmol) N,N-bis(t-butyloxycarbonylmethyl)-2-(bromethyl)-amine, and this is stirred intensively for 2 hours at room temperature. One then separates the buffer phase, one extracts it with 10 ml of acetonitrile and one adds the latter to the organic phase. After adding 20 ml of fresh buffer, one stirs for another 20 hours at room temperature. One separates the organic phase, one concentrates it and distributes the residue between 100 ml of phosphate buffer (pH 8.0) and 100 ml of acetic ester. The organic phase is washed with common salt solution, it is dried over sodium sulfate and it

is concentrated. The title compound is obtained by chromatography on silica gel. Dichloromethane with an increasing addition of methanol is used as eluent. The title compound is obtained in the form of a glass-like solid.

Yield: 4.161 g (78.4% of theoretical).

Elementary analysis:

Calculated:	C 45.20	H 5.59	F 30.39	N 5.27
Found:	C 45.35	H 5.67	F 30.47	N 5.34

d) 3,9-bis(carboxymethyl)-6-N-(1H,1H,2H,2H-perfluorodecyl)-aminocarbonylmethyl-3,6,9-triazaundecanic-diacid

Into a mixture of 100 ml of trifluoracetic acid/dichloromethane in a ratio of 2:1, one adds 4.783 g (4.5 mmol) of the compound made according to 25c). One stirs overnight at room temperature, one concentrates to dryness, one removes the residues of trifluoracetic acid by codistillation with ethanol and one then absorbs in 160 ml of a mixture consisting of water, ethanol and chloroform (10:5:1). A pH value of about 3 (pH constancy) is adjusted by adding ion exchanger IR A-67 (OH^- form). One suctions off quickly, one concentrates and one obtains the title compound in the form of a glassy solid./103

Yield: 3.007 g (79.7% of theoretical).

Water content: 10.9%.

Elementary analysis:

Calculated:	C 34.38	H 3.25	F 38.52	N 6.68
Found:	C 34.29	H 3.33	F 38.65	N 6.77

e) Gadolinium complex, monosodium salt of 3,9-bis(carboxymethyl)-6-N-(1H,1H,2H,2H-perfluorodecyl)-aminocarbonylmethyl)-3,6,9-triazaundecanic-diacid

Into a mixture of 60 ml of distilled water and 30 ml of ethanol, one adds 2.823 g (3.0 mmol calculated on the basis of 10.9% water content) of the acid made under 25d). While stirring and heating to 50°C, one adds 543.8 mg (1.5 mmol) of gadolinium oxide in portions. After the addition has been completed, one stirs until solution. Then one sets the pH value of the solution at 7.2 by adding caustic soda. The solution is concentrated. This is accompanied by intensive foaming. The residue is codistilled twice with distilled water. The title compound is obtained in the form of a glassy solid.

Yield: 3.353 g (quantitative).

Water content: 9.2%.

The elementary analysis is calculated for anhydrous substance.

Calculated: C 28.41 H 2.28 F 31.83 Gd 15.50 N 5.52 Na 2.27

Found: C 28.51 H 2.33 F 31.76 Gd 15.57 N 5.46 Na 2.35

Example 26

Gadolinium complex, disodium salt of 3,6,9-tris(carboxymethyl)-4-[N-1H,1H,2H,2H-perfluorodecyloxy)-benzyl]-3,6,9-triaza-undecanic-diacid

a) 3,6,9-tris-(t-butyloxycarbonylmethyl)-4-[4-(1H,1H,2H,2H-perfluorodecyloxy)-benzyl]-3,6,9-triazaundecanic-diacid-di(t-butylester) /104

Into 50 ml of dry dimethylformamide, one adds 6.131 g (5 mmol) of 3,6,9-tris(t-butyloxycarbonylmethyl)-4-(4-hydroxybenzyl)-3,6,9-triaazaundecanic-diacid-di(t-butylester), made according to PCT WO 88/07521 and are mixed in portions while stirring and with the exclusion of moisture with 150 g (5 mmol) of sodium hydride (80% in oil). After dissolution, one mixes with 3.092 g (5 mmol) of the tosylate made according to Example 7a). One stirs for 12 hours at 40°C. Then one pours in 500 ml of ice water, one absorbs the product in dichloromethane, one washes the organic solution with water, one dries over sodium sulfate and one concentrates all the way to dryness. The residue is purified by means of chromatography on silica gel. A mixture of dichloromethane, isopropanol, hexane in a ratio of 20:1:5 is used as eluent.

The title compound is obtained in the form of an amorphous solid.

Elementary analysis:

Calculated:	C 49.96	H 5.92	F 26.34	N 3.43
Found:	C 50.11	H 6.00	F 26.43	N 3.38

b) 3,6,9-tris(carboxymethyl)-4-[4-(1H,1H,2H,2H-perfluorodecyloxy)-benzyl]-3,6,9-triazaundecanic-diacid

Into 100 ml of a mixture of trifluoracetic acid and dichloromethane in a ratio of 2:1, one dissolves 3.678 g (3 mmol) of the compound made according to Example 26a) and it is stirred overnight at room temperature. One concentrates to dryness and one removes the residues of trifluoracetic acid by codistillation

with ethanol. One absorbs the residue in 160 ml of a mixture consisting of water, ethanol and chloroform (10:5:1). The solution is set at a pH value of about 3 (pH constancy) by adding ion exchanger IRA-67 (OH^- form). One suctions off quickly, one concentrates and one gets the title compound in the form of a glassy solid.

Yield: 2.357 g (83.1% of theoretical).

Water content: 11.3%.

The elementary analysis is calculated for anhydrous substance. /105

Calculated:	C 39.38	H 3.41	F 34.16	N 4.44
Found:	C 39.52	H 3.47	F 34.32	N 4.36

Gadolinium complex, disodium salt of 3,6,9-tris(carboxymethyl)-4-[N-(1H,1H,2H,2H-perfluorodecyloxy)-benzyl]-3,6,9-triaza-undecanic-diacid

Into a mixture of 60 ml of distilled water and 30 ml of ethanol, one adds 3.145 g (3.0 mmol calculated on the basis of 11.3% water content) of the acid made under 26d). While stirring and heating to 50°C, one adds 543.8 mg (1.5 mmol) of gadolinium oxide in portions. After the addition has been completed, one stirs until solution. Then one sets the pH value of the solution at 7.2 by adding caustic soda and one concentrates. This is accompanied by intensive foaming. The residue is codistilled twice with distilled water. The title compound is obtained in the form of a glassy solid.

Yield: 3.804 g (quantitative).

Water content: 9.8%.

Elementary analysis (related to anhydrous substance):

Calculated: C 32.55 H 2.38 F 28.24 Gd 13.75 N 3.67 Na 4.02

Found: C 32.44 H 2.43 F 28.30 Gd 13.66 N 3.71 Na 4.10

Example 27

Gadolinium complex of 10-[(-perfluoroctyl-sulfonyl)-piperazine-1-yl-carbonylmethyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

a) 1-perfluoroctylsulfonyl-piperazine

34.39 g (398,3 mmol) of piperazine, 50 g (99.6 mmol) of perfluoroctylsulfonyl fluoride and 10.12 g (100 mmol) of triethylamine are heated for 24 hours at 85°C. One adds 500 ml of water and extracts twice with 200 ml of dichloromethane each. The organic phase is dried over magnesium sulfate and is evaporated to dryness in a vacuum. The residue is chromatographed on silica gel (process agent: dichloromethane/2-propanol = 25:1). /106

Yield: 17.55 g (31% of theoretical) of a colorless amorphous solid.

Elementary analysis:

Calculated:	C 25.36	H 1.60	F 56.84	N 4.93	S 5.64
Found:	C 25.15	H 1.80	F 56.65	N 4.81	S 5.70

b) 1-(2-bromacetyl)-4-perfluoroctylsulfonyl-piperazine

17 g (29.9 mmol) of the title compound from Example 27a) and 5.1 g (50 mmol) of triethylamine are dissolved in 100 ml of dichloromethane. At -10°C over a period of 30 minutes, one drips

in 9.1 g (44.9 mmol) of bromacetyl bromide and one stirs for 2 hours at 0°C. One pours the solution into 200 ml of 2N hydrochloric acid and one stirs thoroughly. The organic phase is separated, it is dried over magnesium sulfate and it is concentrated in a vacuum. The residue is chromatographed on silica gel (process agent: dichloromethane/acetone = 20/1).

Yield: 18.55 g (90% of theoretical) of a slightly yellow-colored, wax-like solid.

Elementary analysis:

Calculated: C 24.40 H 1.46 F 46.86 N 4.06 S 4.65 Br 11.59

Found: C 24.22 H 1.60 F 46.75 N 3.97 S 4.48 Br 11.41

c) 10-[(-perfluoroctyl-sulfonyl)-piperazine-1-yl-carbonylmethyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

To 17.78 g (20 mmol) of the title compound from Example 27b), in 180 ml of methanol, one adds 4.63 g (13.36 mmol) of 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (≙ DO3A) and 18.5 g (133.6 mmol) potassium carbonate. One boils for 12 hours under reflux. The inorganic salts are filtered off and the filtrate is evaporated to dryness. The residue is absorbed in 100 ml of water and is set at a pH of 3 with 5N hydrochloric acid. One extracts twice with 150 ml of n-butanol. The combined organic phases are concentrated to dryness in a vacuum and the residue is purified by means of RP chromatography (RP-18/process agent = gradient from water/n-butanol/acetonitrile). /107

Yield: 12.79 g (67% of theoretical) of a colorless solid.

Water content: 8.5%.

Elementary analysis:

Calculated:	C 35.23	H 3.70	F 33.83	N 8.80	S 3.36
Found:	C 35.17	H 3.81	F 33.67	N 8.65	S 3.18

d) Gadolinium complex of 10-[(-perfluoroctyl-sulfonyl)-piperazine-1-yl-carbonylmethyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

10 g (10.47 mmol) of the title compound from Example 27c) are dissolved in a mixture of 50 ml of water/20 ml of ethanol and 1.90 g (5.23 mmol) of gadolinium oxide are added. One stirs for 4 hours at 80°C. The solution is filtered and is evaporated to dryness in a vacuum.

Yield: 12.2 g (quantitative).

Water content: 5.1%.

Elementary analysis:

Calculated:	C 30.33	H 2.91	F 29.13	Gd 14.18	S 2.89
Found:	C 30.39	H 2.81	F 29.02	Gd 14.01	S 2.78

Example 28

Gadolinium complex, monosodium salt of 3,9-bis(carboxymethyl)-6-[(4-perfluorosulfonyl)-piperazine-1-carbonylmethyl]-3,6,9-triaazaundecanic-diacid

a) 1-(2-benzyloxycarbonylamino)-methyl-carbonyl-4-(perfluoroctylsulfonyl)-piperazine

In 80 ml of dichloromethane, one adds 8.524 g (15 mmol) of the piperazine derivative made according to 27a) and 1.726 g (15 mmol) of N-hydroxysuccinimide, 3.095 g (15 mmol) of

dicyclohexylcarbodiimide and 3.138 g (15 mmol) of N-benzyloxycarbonylglycine (brand name Bachem). One stirs overnight, one filters the dicyclohexylurea off, one concentrates and subjects the residue to column chromatography on silica gel. Mixtures of dichloromethane and ethanol are used as eluents. The title compound is obtained in the form of a solid. /108

Yield: 10.16 g (89.2% of theoretical).

Elementary analysis:

Calculated:	C 34.79	H 2.39	F 42.53	N 5.53	S 4.22
Found:	C 34.60	H 2.43	F 42.65	N 5.66	S 4.17

b) 1-(2-amino)-acetyl-4-(perfluoroctyl)-sulfonyl-piperazine

In 150 ml of a mixture of tetrahydrofurane and ethanol in a ratio of 2:1, one adds 7.594 g (10 mmol) of the compound made according to 28a) and are hydrated in the presence of 0.25 g of Pearlman catalyst (Pd 20%/C) up to the absorption of 224 ml of hydrogen. One suctions off the catalyst, one washes thoroughly with ethanol and one concentrates to dryness. The title compound is obtained in the form of an amorphous solid.

Yield: 6.21 g (99.3% of theoretical).

Elementary analysis:

Calculated:	C 26.89	H 1.93	F 51.65	N 6.72	S 5.13
Found:	C 27.03	H 1.97	F 51.77	N 6.58	S 5.20

c) 3,9-bis(t-butylcarbonylmethyl)-6-[(4-perfluoroctylsulfonyl)-piperazine-1-carbonylmethyl]-3,6,9-triaazaundecanic-diacid-di(t-butylester)

Into a mixture of 10 ml of acetonitrile and 20 ml of phosphate buffer with a pH value of 8.0, one dissolves 3.127 g (5 mmol) of the amine made according to 28b) and 3.875 g (11 mmol) of N,N-bis(t-butyloxycarbonylmethyl)-2-(bromethyl)-amine and one stirs intensively for 2 hours at room temperature. One then separates the buffer, one extracts with 10 ml of acetonitrile and one adds the latter to the organic phase. After the addition of 20 ml of fresh buffer, one stirs another 20 hours at room temperature. One separates the organic phase, one concentrates it and one distributes the residue between 100 ml of phosphate buffer (pH 8.0) and 100 ml of acetic ester. The organic phase is washed with saturated common salt solution, it is dried over sodium sulfate and concentrated. The title compound is purified by chromatography on silica gel. Dichloromethane with an increasing addition of methanol is used as eluent. The title compound is obtained in the form of a glassy solid. /109

Yield: 4.481 g (76.3% of theoretical).

Elementary analysis:

Calculated:	C 43.71	H 5.42	F 27.99	N 4.85	S 2.78
Found:	C 43.84	H 5.47	F 28.10	N 5.00	S 2.69

b) 3,9-bis(carboxymethyl)-6-[(4-perfluoroctylsulfonyl)-piperazine-1-yl-carbonylmethyl]-3,6,9-triazaundecanic-diacid

Into 100 ml of a mixture of trifluoracetic acid and dichloromethane in a ratio of 2:1, one dissolves 5.193 g (4.5 mmol) of the compound made according to Example 28c). One continues stirring overnight at room temperature, whereupon one

concentrates to dryness, one removes the residues of trifluoracetic acid by codistillation with ethanol and one absorbs in 160 ml of a mixture consisting of water, ethanol and chloroform (10:5:1). The solution is set at a pH value of about 3 (pH constancy) by adding ion exchanger IRA-67 (OH^- form). One suctions off quickly, one concentrates and one gets the title compound in the form of a glassy solid.

Yield: 3.718 g (79.2% of theoretical).

Water content: 10.9%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 33.59	H 3.25	F 34.74	N 6.03	S 3.45
Found:	C 33.69	H 3.36	F 34.82	N 6.10	S 3.38

e) Gadolinium complex, monosodium salt of 3,9-bis(carboxymethyl)-6-[(4-perfluorosulfonyl)-piperazine-1-carbonylmethyl]-3,6,9-triaazaundecanic-diacid

Into a mixture of 60 ml of distilled water and 30 ml of ethanol, one adds 3.13 g (3.0 mmol calculated on the basis of 10.9% water content) of the acid made under 28d). While stirring and heating to 50°C, one adds 543.8 mg (1.5 mmol) of gadolinium oxide in portions. After the addition has been completed, one stirs until solution. Then one sets the pH value of the solution at 7.2 by adding caustic soda and one concentrates. This is accompanied by intensive foaming. The residue is codistilled twice with distilled water. The title compound is obtained in the form of a glassy solid. /110

Yield: 3.678 g (quantitative).

Water content: 9.2%.

Elementary analysis (related to anhydrous substance):

Calc: C 28.24 H 2.37 F 29.21 Gd 14.22 N 5.07 Na 2.08 S 2.90

Found: C 28.36 H 2.41 F 29.14 Gd 14.30 N 5.15 Na 2.12 S 2.83

Example 29

Gadolinium complex of 3,6,9-tris(carboxymethyl)-3,6,9-triaazaundecanic-diacid-bis[(4-perfluoroctylsulfonyl)-piperazine]-amide

a) 3,6,9-tris(carboxymethyl)-3,6,9-triaazaundecanic-diacid-bis[(4-perfluoroctylsulfonyl)-piperazine]-amide

In 30 ml of dry dimethylformamide, one adds 5.683 g (10 mmol) of the compound made according to 27a) as well as 1.518 g (15 mmol) of triethylamine and are mixed in portions while stirring and excluding moisture with 1.787 g (5 mmol) of diethylenetriaminepenta-acetic-acid-bisanhydride. One stirs overnight, one concentrates, mixes with water, sets the pH value at about 3 with the help of 3N hydrochloric acid and extracts twice with 100 ml of N-butanol each. The organic solutions are combined, concentrated and subjected to chromatography on RP-18 silica gel. Water and tetrahydrofurane are used as eluent. The title compound is obtained in the form of a glass-like solid.

Yield: 6.741 g (81.4% of theoretical).

Water content: 9.8%. /111

Elementary analysis (related to anhydrous substance):

Calculated:	C 30.55	H 2.50	F 43.24	N 6.56	S 4.29
Found:	C 30.67	H 2.55	F 43.33	N 6.49	S 4.21

b) Gadolinium complex of 3,6,9-tris(carboxymethyl)-3,6,9-triazaundecanic-diacid-bis-[(4-perfluoroctylsulfonyl)-piperazine-amide

Into a mixture of 120 ml of distilled water, 60 ml of ethanol and 20 ml of chloroform, one adds 6.570 g (4 mmol calculated on the basis of 9.8% water content) of the compound made under 23c). While stirring and heating to 50°C, one adds 725 mg (82.0 mmol) of gadolinium oxide in portions. One stirs until solution, one concentrates, which is accompanied by intensive foaming, and one subjects the residue to codistillation with distilled water. Codistillation is repeated twice. The title compound is obtained in the form of a glass-like solid.

Yield: 7.191 g (quantitative).

Water content: 8.1%.

Elementary analysis (related to anhydrous substance):

Calculated: C 27.69 H 2.08 F 39.19 Gd 9.54 N 5.95 S 3.89

Found: C 27.83 H 2.15 F 39.10 Gd 6.91 N 6.03 S 3.88

Example 30

a) 11-[N-ethyl-N-(perfluoroctylsulfonyl)-amino]undecanic acid benzyl ester

20 g (37.94 mmol) of N-ethyl-N-perfluoroctylsulfonamide and 15.73 g (113.8 mmol) of potassium carbonate are suspended in 200 ml of acetone and 26.96 g (75.87 mmol) of 11-bromundecanic acid benzyl ester are dripped in at 60°C. One stirs for 3 hours at 60°C. One filters off the salts and one evaporates the filtrate in a vacuum to dryness. The residue is chromatographed on silica

gel (process agent: hexane/dichloromethane/acetone = 1/10/1). One recrystallizes the residue from methanol/ether after the evaporation of the product-containing fractions.

Yield: 26.46 g (87% of theoretical) of a colorless, crystalline powder. 112

Elementary analysis:

Calculated:	C 41.95	H 4.02	N 1.75	F 40.29	S 4.00
Found:	C 41.78	H 4.17	N 1.68	F 40.12	S 3.88

b) 11-[N-ethyl-N-(perfluoroctylsulfonyl)-aminoundecanic acid

20 g (24.95 mmol) of the title compound from Example 30a) is dissolved in 300 ml of isopropanol/200 ml of dichloromethane and one adds 3 g of palladium catalyst (10% Pd/C). One hydrates overnight at room temperature. One filters off the catalyst and the filtrate is evaporated to dryness in a vacuum. The residue is recrystallized from ether/hexane.

Yield: 16.69 g (94% of theoretical) of a colorless, crystalline solid.

Elementary analysis:

Calculated:	C 35.45	H 3.68	N 1.97	F 45.39	S 4.51
Found:	C 35.31	H 3.81	N 1.85	F 45.25	S 4.42

c) Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-16-aza-16-(perfluoroctylsulfonyl-octadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

12.16 g (17.09 mmol) of the title compound from Example 30b) and 1.87 g (18.79 mmol) of N-hydroxysuccinimide are dissolved in a mixture of 50 ml dimethylformamide/50 ml of chloroform. At

0°C, one adds 3.88 g (18.79 mmol) of dicyclohexylcarbodiimide and one stirs for 1 hour at 0°C, and after that, for 3 hours at room temperature. One again cools down to 0°C and one adds 5.19 g (51.27 mmol) of triethylamine/50 ml of 2-propanol. Then one adds 10.78 g (18.79 mmol) of gadolinium complex of 10-(3-amino-2-hydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (WO 95/17451) dissolved in 50 ml of water and one stirs for 3 hours at room temperature. One evaporates to dryness, one absorbs the residue in a mixture of 200 ml of methanol/100 ml of chloroform and one filters off the dicyclohexylurea. The filtrate is evaporated to dryness and is purified by RP chromatography (RP-18/process agent: gradient from water/N-propanol/acetonitrile). /113

Yield: 16.82 g (71% of theoretical) of a colorless, glassy solid.

Water content: 8.6%.

Elementary analysis (related to anhydrous substance):

Calculated: C 36.02 H 4.30 F 25.49 Gd 12.41 N 6.63 S 2.53

Found: C 35.87 H 4.45 F 25.28 Gd 12.29 N 6.50 S 2.41

d) 10-[2-hydroxy-4-aza-5-oxo-16-aza-16-(perfluoroctylsulfonyl-octadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

11.1 g (8.76 mmol) of the title compound from Example 30c) is dissolved in a mixture of 100 ml of water/100 ml of ethanol and 1.73 g (13.71 mmol) of oxalic acid dihydrate. One heats for 8 hours to 80°C. One cools down to 0°C and one filters off the

precipitated gadolinium oxalate. The filtrate is evaporated to dryness and the residue is purified on RP-18 (RP-18/process agent: gradient from water/i-propanol/acetonitrile).

Yield: 9.80 g (82% of theoretical) of a glassy solid.

Water content: 8.5%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 41.01	H 5.16	F 29.02	N 7.55	S 2.88
Found:	C 40.87	H 5.31	F 28.85	N 7.40	S 2.73

e) Ytterbium complex of 10-[2-hydroxy-4-aza-5-oxo-16-aza-16-(perfluoroctylsulfonyl-octadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane /114

To 5.64 g (5.07 mmol) of the title compound from Example 30d) in 100 ml of water/50 ml of ethanol, one adds 1.33 g (2.53 mmol) of ytterbium carbonate and one stirs for 3 hours at 80°C.

The solution is filtered and the filtrate is evaporated to dryness in the vacuum.

Yield: 7.08 g (quantitative) of a glassy solid.

Water content: 8.1%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 35.58	H 4.24	F 25.17	N 6.55	S 2.50	Yb 13.49
Found:	C 35.43	H 4.37	F 25.05	N 6.48	S 2.39	Yb 13.35

f) Dysprosium complex of 10-[2-hydroxy-4-aza-5-oxo-16-aza-16-(perfluoroctylsulfonyl-octadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

To 5.64 g (5.07 mmol) of the title compound from Example 30d) in 100 ml of water/50 ml of ethanol, one adds 0.95 g (2.53

mmol) of dysprosium oxide and one stirs for 3 hours at 80°C. The solution is filtered and the filtrate is evaporated to dryness in the vacuum.

Yield: 7.10 g (quantitative) of a colorless, glassy solid.

Water content: 9.1%.

Elementary analysis (related to anhydrous substance):

Calculated: C 35.87 H 4.28 F 25.38 N 6.60 S 2.52 Dy 12.77

Found: C 35.69 H 4.39 F 25.18 N 6.49 S 2.43 Dy 12.70

Example 31 /115

a) 11,11,11,10,10,9,9,8,8,7,7-tridecafluor-3-oxaundecanic acid-tert.-butyl ester

To a mixture consisting of 27.57 g (75.73 mmol) of 1H,1H,2H,2H-perfluoroctane-1-ol and 2.57 g (7.57 mmol) of tetrabutylammonium hydrogen sulfate in 300 ml of 60% aqueous caustic potash solution/200 ml of toluene, one drips in, while stirring forcefully at 0°C, 19.51 g (100.0 mmol) of bromacetic acid-tert.-butyl ester. One stirs for 1 hour at 0°C, one separates the organic phase and one extracts the aqueous phase twice with 50 ml of toluene. The combined organic extracts are dried over sodium sulfate and are evaporated in a vacuum. The residue is chromatographed on silica gel (process agent: dichloromethane).

Yield: 28.97 g (87% of theoretical) of a colorless oil.

Elementary analysis:

Calculated: C 35.16 H 3.16 F 51.64

Found: C 35.08 H 3.20 F 51.70

b) 11,11,11,10,10,9,9,8,8,7,7-tridecafluor-3-oxaundecanic acid

25.29 g (52.88 mmol) of the title compound from Example 1a) is dissolved in 300 ml of trifluoracetic acid and is stirred overnight at room temperature. One evaporates to dryness in a vacuum and one recrystallizes the residue from hexane/diethylether.

Yield: 20.54 g (92% of theoretical) of a colorless crystalline solid.

Elementary analysis:

Calculated:	C 28.45	H 1.67	F 58.51
Found:	C 28.36	H 1.60	F 58.62

c) Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-oxa-10,10,11,11,12,12,13,13,14,14,15,15,15-tridecafluor-pentadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane /116

7.21 g (17.09 mmol) of the title compound from Example 31b) and 1.97 g (18.79 mmol) of N-hydroxysuccinimide are dissolved in a mixture consisting of 50 ml of dimethylformamide/50 ml of chloroform. At 0°C, one adds 3.88 g (18.79 mmol) of dicyclohexylcarbodiimide and one stirs for 1 hour at 0°C, and then for 3 hours at room temperature. One again cools down to 0°C and one adds 5.19 g (51.27 mmol) of triethylamine/50 ml of 2-propanol. Then one adds 10.78 g (18.79 mmol) of gadolinium complex of 10-(3-amino-2-hydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (WO 95/17451) dissolved in 50 ml of water and one stirs for 3 hours at room

temperature. One evaporates to dryness, one absorbs the residue in a mixture of 200 ml of methanol/100 ml of chloroform and one filters off the dicyclohexylurea. The filtrate is evaporated to dryness and is purified by RP chromatography (RP-18/process agent: gradient from water/N-propanol/acetonitrile).

Yield: 12.68 g (71% of theoretical) of a colorless, glassy solid.

Water content: 6.4%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 33.16	H 3.61	F 25.26	Gd 16.08	N 7.16
Found:	C 32.85	H 3.84	F 25.01	Gd 15.87	N 7.03

Example 32

a) 15,15,14,14,13,13,12,12,11,11,10,10,9,9,8,8,7,7-henicosafluor-3-oxapentadecanic acid-tert.-butyl ester

To a mixture of 42.72 g (75.73 mmol) of 1H,1H,2H,2H-perfluoroctane-1-ol and 2.57 g (7.57 mmol) of tetrabutylammonium hydrogen sulfate in 300 ml of 60% aqueous caustic potash solution/200 ml of toluene, one drips in, while stirring forcefully at 0°C, 19.51 g (100.0 mmol) of bromacetic acid-tert.-butyl ester. One stirs for 1 hour at 0°C, one separates the organic phase and one extracts the aqueous phase twice with 50 ml of toluene. The combined organic extracts are dried over sodium sulfate and are evaporated in a vacuum. The residue is chromatographed on silica gel (process agent: dichloromethane). /117

Yield: 42.18 g (82% of theoretical) of a colorless oil.

Elementary analysis:

Calculated:	C 31.87	H 2.23	F 58.82
Found:	C 31.73	H 2.20	F 58.90

b) 15,15,14,14,13,13,12,12,11,11,10,10,9,9,8,8,7,7-henicosafluor-3-oxapentadecanic-tert.-butyl ester

35.87 g (52.88 mmol) of the title compound from Example 1a) is dissolved in 300 ml of trifluoracetic acid and stirred overnight at room temperature. One evaporates to dryness in a vacuum and one recrystallizes the residue from hexane/diethylether.

Yield: 30.60 g (93% of theoretical) of a colorless crystalline solid.

Elementary analysis:

Calculated:	C 27.03	H 1.13	F 64.12
Found:	C 26.91	H 1.20	F 64.02

c) Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-oxa-10,10,11,11,12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19-henicosafluor-nonadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

10.63 g (17.09 mmol) of the title compound from Example 32b) and 1.97 g (18.79 mmol) of N-hydroxysuccinimide are dissolved in a mixture consisting of 50 ml of dimethylformamide/50 ml of chloroform. At 0°C, one adds 3.88 g (18.79 mmol) of dicyclohexylcarbodiimide and one stirs for 1 hour at 0°C, and then for 3 hours at room temperature. One again cools down to 0°C and one adds 5.19 g (51.27 mmol) of triethylamine/50 ml of 2-

propanol. Then one adds 10.78 g (18.79 mmol) of gadolinium complex of 10-(3-amino-2-hydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (WO 95/17451) dissolved in 50 ml of water and one stirs for 3 hours at room temperature. One evaporates to dryness, one absorbs the residue in a mixture of 200 ml of methanol/100 ml of chloroform and one filters off the dicyclohexylurea. The filtrate is evaporated to dryness and is purified by RP chromatography (RP-18/process agent: gradient from water/N-propanol/acetonitrile). /118

Yield: 14.73 g (69% of theoretical) of a colorless, glassy solid.

Water content: 5.7%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 31.61	H 2.99	F 33.87	Gd 13.35	N 5.95
Found:	C 31.49	H 3.15	F 33.68	Gd 13.21	N 6.01

Example 33

a) N-(2-bromopropionyl)glycine-benzyl ester

To 100 g (296.4 mmol) of glycine benzyl ester-p-toluene sulfonic acid salt and 33.0 g (326.1 mmol) of triethylamine in 400 ml of methylene chloride, one drips in at 0°C 55.9 g (326.1 mmol) of 2-bromopropionic acid chloride. One does not let the temperature rise above 5°C. After addition has been completed, one stirs for 1 hour at 0°C and then for 2 hours at room temperature. One adds 500 ml of ice water and one adjusts the water phase at a pH of 2 with 10% aqueous hydrochloric acid. The organic phase is separated, it is washed once each with 300 ml of

5% aqueous soda solution and 400 ml of water. One dries the organic phase over magnesium sulfate and one evaporates to dryness in a vacuum. The residue is recrystallized from diisopropyl ether.

Yield: 68.51 g (75% of theoretical) of a colorless, crystalline powder.

Melting point: 69-70°C. /119

Elementary analysis:

Calculated:	C 48.02	H 4.70	N 4.67	Br 26.62
Found:	C 47.91	H 4.82	N 4.51	Br 26.47

b) 1-[-4-(benzyloxycarbonyl)-1-methyl-2-oxo-3-azabutyl]-1,4,7,10-tetraazacyclododecane

To 55.8 g (324.4 mmol) of 1,4,7,10-tetraazacyclododecane dissolved in 600 ml of chloroform, one adds 50 g (162.2 mmol) of the title compound from Example 1a) and one stirs overnight at room temperature. One adds 500 ml of water, one separates the organic phase and one washes it twice with 400 ml of water. One dries the organic phase over magnesium sulfate and one evaporates to dryness in a vacuum. The residue is chromatographed on silica gel (process agent: chloroform/methanol/aqueous 25% ammonia = 10/5/1).

Yield: 40.0 g [63% of theoretical related to 1a) that is employed] of a slightly yellowish, viscous oil.

Elementary analysis:

Calculated:	C 61.36	H 8.50	N 17.89
Found:	C 61.54	H 8.68	N 17.68

c) 10-[4-benzyloxycarbonyl)-1-methyl-2-oxo-3-azabutyl]-1,4,7-tris(tert.-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (sodium bromide complex)

To 20 g (51.08 mmol) of the title compound from Example 1b) and 17.91 (169 mmol) of sodium carbonate in 300 ml of acetonitrile, one adds 33 g (169 mmol) of bromacetic acid-tert.-butylester and one stirs for 24 hours at 60°C. One cools down to 0°C, one filters off the salt, and one evaporates the filtrate to dryness. The residue is chromatographed on silica gel (process agent: acetic acid ethyl ester/ethanol: 15/1). The fractions containing the production are evaporated and the residue is recrystallized to diisopropyl ether.

Yield: 34.62 g (81% of theoretical) of a colorless crystalline powder. /120

Melting point: 116-117°C

Elementary analysis:

Calculated:	C 54.54	H 7.59	N 8.37	Na 2.74	Br 9.56
Found:	C 54.70	H 7.65	N 8.24	Na 2.60	Br 9.37

d) 10-[4-carboxy-1-methyl-2-oxo-3-azabutyl]-1,4,7-tris(tert.-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (sodium bromide complex)

30 g (35.85 mmol) of the title compound from Example 1c) is dissolved in 500 ml of isopropanol and one adds 3 g of palladium catalyst (10% Pd/C). One hydrates overnight at room temperature. One filters off the catalyst, the filtrate is evaporated to dryness in a vacuum and is recrystallized from acetone.

Yield: 22.75 g (85% of theoretical) of a colorless, crystalline powder.

Melting point: 225°C (decomposition).

Elementary analysis:

Calculated:	C 49.86	H 7.69	N 9.38	Na 3.07	Br 10.71
Found:	C 49.75	H 7.81	N 9.25	Na 2.94	Br 10.58

e) 10-[1-methyl-2-oxo-3-aza-5-oxo-5-{4-perfluoroctylsulfonyl-piperazine-1-yl}-pentyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

10 g (13.39 mmol) of the title compound from Example 33d) and 7.61 g (13.39 mmol) of the title compound from Example 27a) are dissolved in 150 ml of tetrahydrofurane. At 0°C, one adds 3.97 g (16.07 mmol) of N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), one stirs for 3 hours at 0°C and then for 12 hours at room temperature. One evaporates to dryness in a vacuum. The residue is absorbed in 150 ml of trifluoracetic acid and is stirred for 12 hours at room temperature. One evaporates to dryness, the residue is dissolved in water and is set at a pH of 3.2 with the help of 10% caustic soda. For purification purposes, one chromatographs on RP-18 (gradient from water/acetonitrile/tetrahydrofurane).

Yield: 9.67 g (63% of theoretical) of a hygroscopic solid. /121

Water content: 10.5%.

Elementary analysis (related to anhydrous substance):

Calculated:	C 36.30	H 3.93	N 9.56	F 31.49	S 3.13

Found: C 36.14 H 3.98 N 9.40 F 31.67 S 3.02

f) Gadolinium complex of 10-[1-methyl-2-oxo-3-aza-5-oxo-5-{4-perfluoroctylsulfonyl-piperazine-1-yl}-pentyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

5 g (4.87 mmol) of the title compound from Example 33e) is dissolved in 60 ml of water and 0.883 g (2.44 mmol) of gadolinium oxide. One stirs for 3 hours at 90°C. The solution is filtered and the filtrate is freeze dried.

Yield: 6.47 g (quantitative) of a voluminous amorphous powder.

Water content: 11.3%.

Elementary analysis (related to anhydrous substance):

Calculated: C 31.56 H 3.16 N 8.31 F 27.37 S 2.72 Gd 13.33

Found: C 31.37 H 3.35 N 8.18 F 27.19 S 2.92 Gd 13.05

Example 34

a) 4-perfluoroctane sulfonyl piperazine-1-yl-pentane-diamic acid

To a suspension of 11.41 g (100.0 mmol) of glutaric acid anhydride in 100 ml of tetrahydrofurane, one drips in, while stirring forcefully at 0°C, a solution of 10.62 g (105.0 mmol) triethylamine and 59.67 g (105.0 mmol) of the title compound from Example 27a) in 50 ml of tetrahydrofurane and one allows it to come up to room temperature overnight. One solidifies the reaction mixture with 100 ml of 2N HCL and one extracts three times with 100 ml of tetrahydrofurane. The combined organic extracts are dried with sodium sulfate, they are filtered and

then concentrated. The residue is recrystallized from 2-propanol/ethyl acetate. /122

Yield: 52.30 g (73% of theoretical) of a colorless, crystalline solid.

Elementary analysis:

Calculated:	C 29.92	H 2.22	N 4.11	F 47.33	S 4.70
Found:	C 29.90	H 2.18	N 4.07	F 47.42	S 4.79

b) Gadolinium complex of 10-[2-hydroxy-4-aza-5,9-dioxo-9-{4-perfluoroctyl)-piperazine-1-yl}-nonyl]-1,4,7-tris(carboxymethyl)-1,4,7,-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

11.66 g (17.09 mmol) of the title compound from Example 34a) and 1.97 g (18.79 mmol) of N-hydroxysuccinimide are dissolved in a mixture of 50 ml of dimethylformamide/50 ml chloroform. At 0°C, one adds 3.88 g (18.79 mmol) dicyclohexylcarbodiimide and stirs for 1 hour at 0°C and then for 3 hours at room temperature. One cools down again to 0°C and one adds 5.19 g (51.27 mmol) of triethylamine/50 ml of 2-propanol. Then one adds 10.78 g (18.79 mmol) of gadolinium complex of 10-(3-amino-2-hydroxypropyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (WO 95/17451) dissolved in 50 ml of water and one stirs for 3 hours at room temperature. One evaporates to dryness, one absorbs the residue in a mixture of 200 ml of methanol/100 ml of chloroform and one filters off dicyclohexylurea. The filtrate is evaporated to dryness and is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-propanol/acetonitrile).

Yield: 16.7 g (73% of theoretical) of a colorless, glassy solid.

Water content: 7.5%.

Elementary analysis (related to anhydrous substance):

Calculated:	C	32.99	H	3.50	F	26.09	Gd	12.70	N 7.92 S 2.59
Found:	C	32.75	H	3.68	F	25.88	Gd	12.55	N 7.84 S 2.63

Example 35 /123

a) N-benzylperfluoroctane sulfonamide

To a mixture of 10.62 g (105.0 mmol) of triethylamine and 10.72 g (100.0 mmol) of benzylamine, one drips in at 80°C and while stirring forcefully 50.21 g (100.0 mmol) of perfluoroctane sulfonyl fluoride. One stirs for 2 days at 80°C, one mixes the reaction mixture with 300 ml of water and one extracts three times with ethyl acetate. The combined organic extracts are dried over sodium sulfate, they are filtered and concentrated. The residue is chromatographed on silica gel (process agent: dichloromethane/methanol = 4/1).

Yield: 45.96 g (78% of theoretical) of a colorless liquid.

Elementary analysis:

Calculated:	C	30.57	H	1.37	N	2.38	S	5.44	F 54.81
Found:	C	30.49	H	1.30	N	2.42	S	5.50	F 54.90

b) N-benzyl-N-(perfluoroctylsulfonyl)-aminoacetic acid-t.-butyl ester

22.4 g (37.94 mmol) of the title compound from Example 35a) and 15.73 g (113.8 mmol) of potassium carbonate are suspended in 200 ml of acetone, and at 60°C, one drips in 14.80 g (75.87 mmol)

bromacetic acid-tert.-butyl ester. One stirs for 3 hours at 60°C. One filters off the salts and one evaporates the filtrate to dryness in the vacuum. The residue is chromatographed on silica gel (process agent: hexane/dichloromethane/acetone = 10/10/1). After evaporation of the product-containing fractions, one recrystallizes the residue from methanol/ether.

Yield: 24.02 g (90% of theoretical) of a wax-like, colorless solid.

Elementary analysis:

Calculated:	C 35.86	H 2.58	N 1.99	S 4.56	F 45.91
Found:	C 35.67	H 2.71	N 2.13	S 4.45	F 45.83

c) N-benzyl-N-(perfluoroctylsulfonyl)-aminoacetic acid

20 g (28.43 mmol) of the title compound from Example 35b) is dissolved in 200 ml of trifluoracetic acid and one stirs overnight at room temperature. One evaporates to dryness in a vacuum. The residue is recrystallized from methanol/ether. /124

Yield: 17.48 g (95% of theoretical) of a colorless, crystalline solid.

Elementary analysis:

Calculated:	C 31.54	H 1.56	N 2.16	S 4.95	F 49.89
Found:	C 31.38	H 1.70	N 2.05	S 4.87	F 49.71

d) Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluoroctylsulfonyl)-8-phenyl-octyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

11.06 g (17.09 mmol) of the title compound from Example 35c) and 1.97 g (18.79 mmol) of N-hydroxysuccinimide are dissolved in

a mixture of 50 ml of dimethylformamide/50 ml chloroform. At 0°C, one adds 3.88 g (18.79 mmol) dicyclohexylcarbodiimide and stirs for 1 hour at 0°C and then for 3 hours at room temperature. One cools down again to 0°C and one adds 5.19 g (51.27 mmol) of triethylamine/50 ml of 2-propanol. Then one adds 10.78 g (18.79 mmol) of gadolinium complex of 10-(3-amino-2-hydroxy-propyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (WO 95/17451) dissolved in 50 ml of water and one stirs for 3 hours at room temperature. One evaporates to dryness, one absorbs the residue in a mixture of 200 ml of methanol/100 ml of chloroform and one filters off dicyclohexylurea. The filtrate is evaporated to dryness and is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-propanol/acetonitrile).

Yield: 16.49 g (75% of theoretical) of a colorless, glassy solid.

Water content: 6.5%.

Elementary analysis:

Calculated: C 33.95 H 3.18 N 6.99 S 2.67 F 26.85 Gd 13.07

Found: C 33.81 H 3.24 N 6.82 S 2.54 F 26.64 Gd 12.91

Example 36 /125

a) N-decylperfluoroctane sulfonamide

To a mixture of 10.62 g (105.0 mmol) of triethylamine and 15.73 g (100.0 mmol) of decylamine, one drips in at 80°C while stirring forcefully 50.21 g (100.0 mmol) of perfluoroctane sulfonyl fluoride. One stirs for 2 days at 80°C, one mixes the reaction mixture with 300 ml of water and one extracts three

times with ethyl acetate. The combined organic extracts are dried over sodium sulfate, they are then filtered and concentrated. The residue is chromatographed on silica gel (process agent: dichloromethane/methanol = 4/1).

Yield: 43.48 g (68% of theoretical) of a colorless, viscous liquid.

Elementary analysis:

Calculated:	C 33.81	H 3.47	N 2.19	S 5.02	F 50.51
Found:	C 33.71	H 3.39	N 2.15	S 4.93	F 50.31

b) N-decyl-N-(perfluoroctylsulfonyl)-aminoacetic acid-t.-butyl ester

24.26 g (37.94 mmol) of the title compound from Example 36a) and 15.73 g (113.8 mmol) of potassium carbonate are suspended in 200 ml of acetone, and at 60°C, one drips in 14.80 g (75.87 mmol) bromacetic acid-tert.-butyl ester. One stirs for 3 hours at 60°C. One filters off the salts and one evaporates the filtrate to dryness in the vacuum. The residue is chromatographed on silica gel (process agent: hexane/dichloromethane/acetone = 10/10/1). After evaporation of the product-containing fractions, one recrystallizes the residue from methanol/ether.

Yield: 24.87 g (87% of theoretical) of a wax-like, colorless solid.

Elementary analysis:

Calculated:	C 38.25	H 4.28	N 1.86	S 4.26	F 42.86
Found:	C 38.09	H 4.41	N 1.74	S 4.10	F 42.67

c) N-decyl-N-(perfluoroctylsulfonyl)-aminoacetic acid

10 g (26.54 mmol) of the title compound from Example 36b) is dissolved in 200 ml of trifluoracetic acid and one stirs overnight at room temperature. One evaporates to dryness in a vacuum. The residue is recrystallized from methanol/ether. /126

Yield: 17.22 g (93% of theoretical) of a colorless, crystalline solid.

Elementary analysis:

Calculated:	C 34.44	H 3.47	N 2.01	S 4.63	F 46.31
Found:	C 34.28	H 3.30	N 1.95	S 4.65	F 46.28

d) Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluoroctylsulfonyl)-heptadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

11.92 g (17.09 mmol) of the title compound from Example 36c) and 1.97 g (18.79 mmol) of N-hydroxysuccinimide are dissolved in a mixture of 50 ml of dimethylformamide/50 ml chloroform. At 0°C, one adds 3.88 g (18.79 mmol) dicyclohexylcarbodiimide and stirs for 1 hour at 0°C and then for 3 hours at room temperature. One cools down again to 0°C and one adds 5.19 g (51.27 mmol) of triethylamine/50 ml of 2-propanol. Then one adds 10.78 g (18.79 mmol) of gadolinium complex of 10-(3-amino-2-hydroxy-propyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (WO 95/17451) dissolved in 50 ml of water and one stirs for 3 hours at room temperature. One evaporates to dryness, one absorbs the residue in a mixture of 200 ml of methanol/100 ml of chloroform and one filters off dicyclohexylurea. The filtrate is evaporated

to dryness and is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-propanol/acetonitrile).

Yield: 16.76 g (71% of theoretical) of a colorless, glassy solid.

Water content: 6.5%.

Elementary analysis:

Calculated:	C	35.46	H	4.18	N	6.71	S	2.5?	F 25.77 Gd 12.55
Found:	C	35.28	H	4.33	N	6.80	S	2.6?	F 25.65 Gd 12.41

Example 37 /127

a) N-hexylperfluoroctane sulfonamide

To a mixture of 10.62 g (105.0 mmol) of triethylamine and 10.12 g (100.0 mmol) of benzylamine, one drips in at 80°C while stirring forcefully 50.21 g (100.0 mmol) of perfluoroctane sulfonyl fluoride. One stirs for 2 days at 80°C, one mixes the reaction mixture with 300 ml of water and one extracts three times with ethyl acetate. The combined organic extracts are dried over sodium sulfate, they are then filtered and concentrated. The residue is chromatographed on silica gel (process agent: dichloromethane/methanol = 4/1).

Yield: 45.50 g (78% of theoretical) of a colorless liquid.

Elementary analysis:

Calculated:	C	38.83	H	2.42	N	2.40	S	5.50	F 55.37
Found:	C	38.29	H	2.39	N	2.44	S	5.55	F 55.50

b) N-hexyl-N-(perfluoroctylsulfonyl)-aminoacetic acid-t.-butyl ester

22.13 g (37.94 mmol) of the title compound from Example 37a) and 15.73 g (113.8 mmol) of potassium carbonate are suspended in 200 ml of acetone, and at 60°C, one drips in 14.80 g (75.87 mmol) bromacetic acid-tert.-butyl ester. One stirs for 3 hours at 60°C. One filters off the salts and one evaporates the filtrate to dryness in the vacuum. The residue is chromatographed on silica gel (process agent: hexane/dichloromethane/acetone = 10/10/1). After evaporation of the product-containing fractions, one recrystallizes the residue from methanol/ether.

Yield: 23.02 g (87% of theoretical) of a wax-like, colorless solid.

Elementary analysis:

Calculated:	C 34.44	H 3.47	N 2.01	S 4.60	F 46.31
Found:	C 34.31	H 3.61	N 1.97	S 4.65	F 46.25

c) N-hexyl-N-(perfluoroctylsulfonyl)-aminoacetic acid

20 g (28.43 mmol) of the title compound from Example 37b) is dissolved in 200 ml of trifluoracetic acid and one stirs overnight at room temperature. One evaporates to dryness in a vacuum. The residue is recrystallized from methanol/ether. /128

Yield: 16.74 g (91% of theoretical) of a colorless, crystalline solid.

Elementary analysis:

Calculated:	C 39.96	H 2.51	N 2.18	S 5.00	F 50.36
Found:	C 29.87	H 2.70	N 2.05	S 4.84	F 50.17

d) Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluoroctylsulfonyl)-tridecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane

10.96 g (17.09 mmol) of the title compound from Example 37c) and 1.97 g (18.79 mmol) of N-hydroxysuccinimide are dissolved in a mixture of 50 ml of dimethylformamide/50 ml chloroform. At 0°C, one adds 3.88 g (18.79 mmol) dicyclohexylcarbodiimide and stirs for 1 hour at 0°C and then for 3 hours at room temperature. One cools down again to 0°C and one adds 5.19 g (51.27 mmol) of triethylamine/50 ml of 2-propanol. Then one adds 10.78 g (18.79 mmol) of gadolinium complex of 10-(3-amino-2-hydroxy-propyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (WO 95/17451) dissolved in 50 ml of water and one stirs for 3 hours at room temperature. One evaporates to dryness, one absorbs the residue in a mixture of 200 ml of methanol/100 ml of chloroform and one filters off dicyclohexylurea. The filtrate is evaporated to dryness and is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-propanol/acetonitrile).

Yield: 16.46 g (75% of theoretical) of a colorless, glassy solid.

Water content: 6.8%.

Elementary analysis:

Calculated: C 33.11 H 3.70 N 7.02 S 2.68 F 26.98 Gd 13.14

Found: C 33.01 H 3.84 N 6.95 S 2.57 F 26.85 Gd 13.03

Example 38 /129

a) 11-[N-ethyl-N-(perfluoroctylsulfonyl)-amino]-hexanic acid benzyl ester

20 g (37.94 mmol) of N-ethyl-N-perfluoroctyl sulfonyl amide and 15.73 g (113.8 mmol) of potassium carbonate are suspended in 200 ml of acetone, and at 60°C, one drips in 21.64 g (75.87 mmol) of bromohexanic acid benzyl ester. One stirs for 3 hours at 60°C. One filters off the salts and one evaporates the filtrate to dryness in the vacuum. The residue is chromatographed on silica gel (process agent: hexane/dichloromethane/acetone = 10/10/1). After evaporation of the product-containing fractions, one recrystallizes the residue from methanol/ether.

Yield: 25.26 g (91% of theoretical) of a colorless, crystalline powder.

Elementary analysis:

Calculated:	C 37.77	H 3.03	N 1.91	S 4.38	F 44.15
Found:	C 37.61	H 3.18	N 1.84	S 4.27	F 44.01

b) 11-[N-ethyl-N-(perfluoroctylsulfonyl)-amino]-hexanic acid

20 g (27.34 mmol) of the title compound from Example 38b) is dissolved in 300 ml of isopropanol/200 ml of dichloromethane and one adds 3 g of palladium catalyst (10% Pd/C). One hydrates overnight at room temperature. One filters off the catalyst and the filtrate is evaporated to dryness in a vacuum. The residue is recrystallized from ether/hexane.

Yield: 16.31 g (92% of theoretical) of a colorless, crystalline solid.

Elementary analysis:

Calculated:	C 29.96	H 2.51	N 2.18	S 5.00	F 50.36
Found:	C 29.81	H 2.70	N 2.09	S 4.93	F 50.14

d) Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-11-aza-11-(perfluoroctylsulfonyl)-tridecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane /130

10.96 g (17.09 mmol) of the title compound from Example 38b) and 1.97 g (18.79 mmol) of N-hydroxysuccinimide are dissolved in a mixture of 50 ml of dimethylformamide/50 ml chloroform. At 0°C, one adds 3.88 g (18.79 mmol) dicyclohexylcarbodiimide and stirs for 1 hour at 0°C and then for 3 hours at room temperature. One cools down again to 0°C and one adds 5.19 g (51.27 mmol) of triethylamine/50 ml of 2-propanol. Then one adds 10.78 g (18.79 mmol) of gadolinium complex of 10-(3-amino-2-hydroxy-propyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (WO 95/17451) dissolved in 50 ml of water and one stirs for 3 hours at room temperature. One evaporates to dryness, one absorbs the residue in a mixture of 200 ml of methanol/100 ml of chloroform and one filters off dicyclohexylurea. The filtrate is evaporated to dryness and is purified by means of RP chromatography (RP-18/process agent: gradient from water/n-propanol/acetonitrile).

Yield: 15.0 g (69% of theoretical) of a colorless, glassy solid.

Water content: 5.9%.

Elementary analysis:

Calculated:	C 33.11	H 3.70	N 7.02	S 2.68	F 26.98	Gd 13.14	
Found:	C 33.01	H 3.83	N 6.91	S 2.49	F 26.83	Gd 13.05	

Example 39

Blood Elimination Kinetics of Contrast Media

The blood elimination kinetics of contrast media were examined on rats (Han. Wistar, Schering SPF, ≈ 250 g of body weight). Following a one-time intravenous application (via a caudal vein) of the substances (dose: 50-100 μmol Me per kg of body weight), the substance concentration in the blood (based on the Gd or Dy content) was determined for this purpose over a period of up to 300 minutes p.i. by means of ICP-AES. The pharmacokinetic parameters: distribution volume (Vss), total clearance (CLtot) and elimination half-life (tβ) were calculated with a special computer program (TOPFIT 2.0; Thomae, Schering, Gödecke) using as basis a single-component or two-component distribution model. /131

Compared to Dy-DTPA (the dysprosium analogon of Magnevist®), the invention-based fluorine compounds (for example, Example 1c) displayed a definitely slower elimination from the blood and, besides, a smaller distribution volume (see Figure 1 and Table 1).

It must be noted that these compounds quite surprisingly have extended retention in the blood area and therefore are suitable as "blood pool contrast media," -- for example, to present blood vessels with suitable techniques -- also in relatively small dosages of ≤ 50 μmol per kg of body weight.

Figure 1:

Elimination from the blood (in terms of % of injected dose) of Dy-DTPA (dose: 100 μmol per kg of body weight, n=3) and of the invention-based fluorine compounds shown in Example 1c) (dose: 50 μmol Gd per kg of body weight, n=2) after one-time intravenous application of the substances in rats (Han Wistar, Schering SPF, ≈ 250 g of body weight).

The Gd and Dy contents in the blood were determined by means of ICP-AES.

Table 1: /132

Pharmacokinetic parameters: Distribution volume (Vss), total clearance (CLtot) and elimination half-life (tβ) of Dy-DTPA and of the invention-based fluorine compounds of Example 1c) (calculated with TOPFIT 2.0; single- or two-compartment model).

	Vss (l/kg)		CL tot (ml/(min*kg))		t b (min)	
	MEAN	SD	MEAN	SD	MEAN	SD
Dy-DTPA	0.17	0.00	9.27	0.60	14.98	0.73
① Beispiel 1c	0.14	0.02	1.07	0.09	95.01	10.37

[Key: 1) Example].

For further details, see text pertaining to Figure 1.

Example 40

Lymph Node Enrichment in Guinea Pigs

Various fluorine-containing gadolinium and manganese complexes were investigated 90 minutes to 24 hours after subcutaneous administration (2.5-10 μmol total gadolinium/kg of body weight, hind paw s.c.) in stimulated guinea pigs (complete Freund-Adjuvant; each time, 0.1 ml i.m. into the right and left

thigh and lower leg; 2 weeks prior to administration of the test substances (with respect to their lymph node enrichment in three successive lymph node stations (popliteal, inguinal, iliacal). The results, listed in Table 2 below, were obtained in this connection (determination of gadolinium concentration by means of ICP-AES):

Table 2 /133

(1) Substanz (2) Beispiel Nr.	(3) Zeitpunkt der Lymphknoten-entnahme (Dosis)	(4) Gadolinium- bzw. Mangan-Konzentration in drei aufeinanderfolgenden Lymphknotenstationen [µmol/l] (5) [% Dosis/g Gewebe]			
		(6) Popliteal	(7) Inguinal	(8) Iliakal	(9) Verhältnis
1c)	4 h (2,5 µmol/kg)	120 µmol/l 17,2 %	29 µmol/l 4,2 %	40 µmol/l 5,6 %	10 : 2,4 : 3,3
2c)	4 h (10 µmol/kg)	435 µmol/l 10,5 %	84 µmol/l 2,0 %	150 µmol/l 3,6 %	10 : 2,0 : 3,5
1e)	90 min (10 µmol/kg	559 µmol/l 15,0 %	224 µmol/l 6,0 %	290 µmol/l 7,8 %	10 : 4,0 : 5,2
3c)	90 min (10 µmol/kg)	880 µmol/l 21,4 %	277 µmol/l 6,7 %	339 µmol/l 8,3 %	10 : 3,1 : 3,9

[Key: 1) Substance; 2) Example No.; 3) Time of lymph node n-sampling (dose); 4) Gadolinium or manganese concentration in three successive lymph node stations; 5) [% dose/g of tissue]; 6) Popliteal; 7) Inguinal; 8) Iliacal; 9) Ratio].

Table 2 shows that there is a high degree of contrast medium enrichment over three successive lymph node stations.

Example 41

Lymph Node Presentation (MRT) After Interstitial Administration of the Contrast Medium

Figure 1 shows magnetic resonance pictures of popliteal and inguinal lymph nodes both before (left side: precontrast medium) and 120 minutes after (right side) of subcutaneous application (guinea pigs, hind paw, interdigital space) of the Gd complex from Example 2c) (labeled as Gd-DO3A-g-aminoamide-perfluoroctyl ether in the illustration) (10 μmol Gd/kg of body weight). The T^1 weighted spin-echo pictures (TR 400 ms, TE 15 ms) clearly show the strong signal rise in the popliteal and inguinal lymph nodes of the injected (straight arrow) in comparison to the noninjected (bent arrow) side of the body or in contrast to the precontrast medium image.

Example 42 /134

Excretion of Contrast Medium After i.p. Administration

After administration of the invention-based perfluorinated gadolinium complex (100 μmol total gadolinium/kg of body weight) into the

intraperitoneal space of the rat, the retention of the metal in the liver as well as in the remaining body was investigated 14 days after application. The fluorine-containing compound 2c) was used in this experiment. After 14 days p.i., the gadolinium concentration in the liver was 0.22, and in the rest of the body, it was 1.1% of the applied dose.

In comparison to that, Gd-DPTA-polylysin as polymeric material is not complete excreted. After 14 days, 7% of the initial dose is still present in the body.

Example 43

Determination of the T^1 Relaxivity of Selected Compounds

The relaxivity of the following compounds was determined with the help of a Minispec pc 20 (20 MHz, 0.47T) at 37°C in water and human plasma and was compared to the relaxivity of Gd-DTPA-polylysin and Magnevist® as comparison substances.

Table 3

/135

(1) Substanz (2) Beispiel Nr.	R^1 (3) [L/mmol·sec] bei 0.47 T und (4) 37° C	
	Wasser (5)	Plasma
1c)	41	49
2c)	19	33
3c)	15,2	27,5
22f)	6,9	20,5
30c)	21,1	26,9
31c)	5,2	29,1
32c)	19,4	24,8
33f)	31,5	35,7
34b)	25,9	24,9
35d)	23,1	34,0
37d)	19,9	n.b.
38c)	23,3	30,5
Vergleichssubstanzen: (6)		
Magnevist®	3,8	4,8
Gd-DTPA-Polylysin 1)	13,1	16,8

[Key: 1) Substance; 2) Example No.; 3) At; 4) And; 5) Water; 6) Comparison substances].

n.b. = not determined

1) from Invest. Radiol. 1992, 346.

Claims /136

1. Perfluoroalkyl-containing compounds having general formula I:

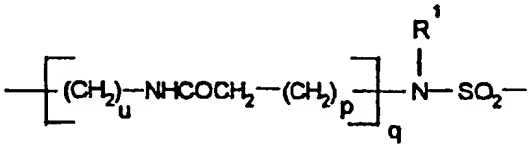
$$R^F\text{-}L\text{-}A \qquad I \qquad (I)$$

where

R^F is a perfluorinated, straight-chain or branched carbon chain with the formula $-C_nF_{2n}X$ where

X is a terminal fluorine, chlorine, bromine, iodine or hydrogen atom and where n represents the numbers from 4 to 30,

L is a direct bond, a methylene group, an -NHCO- group, a group:



where p signifies the numbers from 0 to 10, q and u, independently of each other, represent the numbers 0 or 1 and

R^1 signifies a hydrogen atom, a methylene group, an $-CH_2$-OH- group, an $-CH_2-CO_2H-$ group or a C_2-C_{15} chain that is possibly interrupted by 1 to 3 oxygen atoms, 1 to 2 >CO groups, or a possibly substituted aryl group and/or substituted with 1 to 4 hydroxyl groups, 1 to 2 C_1-C_4 alkoxy groups, 1 to 2 carboxy groups, one group $-SO_3H-$,

or is a straight-chained, branched, saturated or unsaturated C_2-C_{30} carbon chain that possibly contains 1 to 10 oxygen atoms, 1 to 3 $-NR^1-$ groups, 1 to 2 sulfur atoms, one piperazine, one $CONR^1$

group, one -NR^1CO- group, one -SO_2- group, one NR^1-CO_2- group, 1 to 2 0-CO- groups, one group

$$—CO—N(T—N(R^1)—SO_2—R^F)—$$

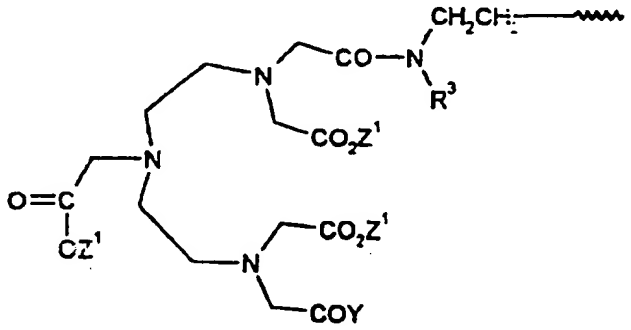
or 1 to 2 possibly substituted aryls and/or is interrupted by these groups and/or is possibly substituted with 1 to 3 -OR^1- groups, 1 to 2 oxo groups, 1 to 2 -NH-COR^1- groups, 1 to 2 -$CONHR^1$- groups, 1 to 2 -(CH_2)-CO_2H- groups, 1 to 2 groups -$(CH_2)_p$-$(O)_q$-CH_2CH_2-R^F, /137

where

R^1, R^F and p and q have the above-mentioned meanings and

T signifies a C_2-C_{10} chain, possibly interrupted by 1 to 2 oxygen atoms or 1 to 2 -NHCO- groups,

A represents a complexing agent or metal complex or their salts of organic and/or inorganic bases or amino acids or amino acid amides specifically representing a complexing agent or a complex having general formula II:



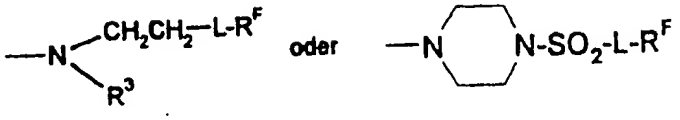
(II)

where R^3, Z^1 and Y are independent of each other and

R^3 has the meaning of R^1 or signifies -$(CH_{2m}$-L-$R^F)$, where m is 0, 1 or 2 and where L and R^F have the above-mentioned meaning,

Z^1 independently of each other signifies a hydrogen atom or a metal ion equivalent of the atomic numbers 1-29, 39, 42, 44 or 57-83,

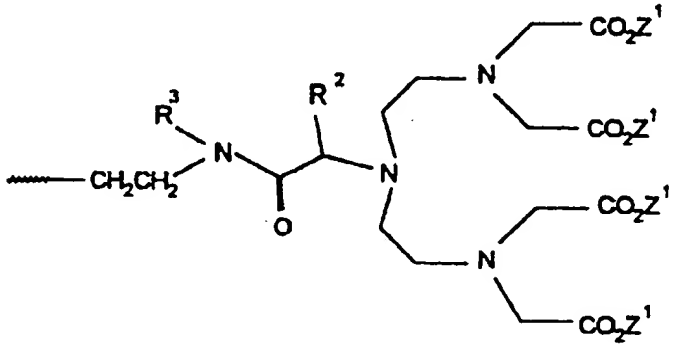
Y $-OZ^1$ or



where Z^1, L, R^F and R^3 have the above-mentioned meaning, /<u>138</u>

or

a complexing agent or complex having general formula III:

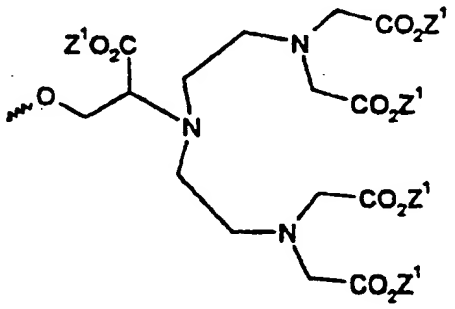


(III)

where R^3 and Z^1 have the above-mentioned meaning and where R^2 has the meaning of R^1

or

a complexing agent or complex having general formula IV:



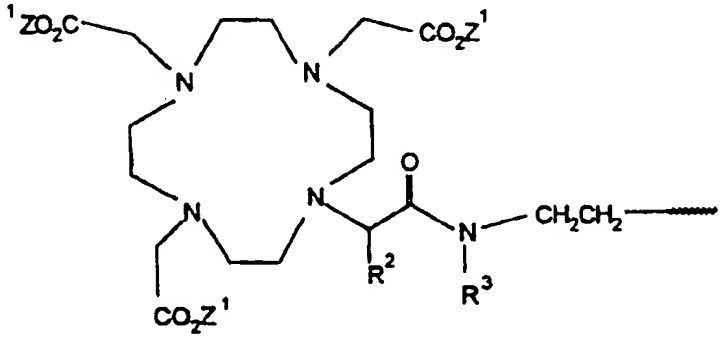
(IV)

where Z^1 has the above-mentioned meaning

where Z^1 and Y have the above-mentioned meanings

or

a complexing agent or complex having general formula VIII: /140

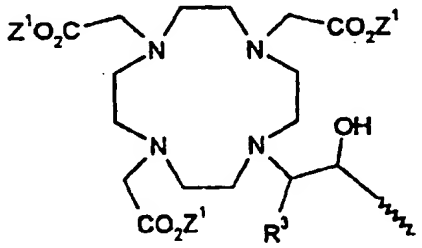


(VIII)

where R^3 and Z^1 have the above-mentioned meanings and R^2 has the above-mentioned meaning of R^1,

or

a complexing agent or complex having general formula IX:

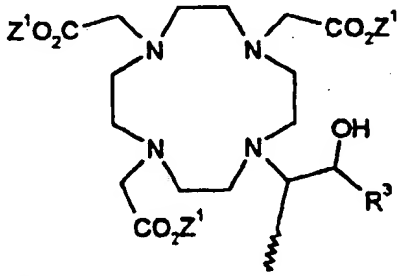


(IX)

where R^3 and Z^1 have the above-mentioned meanings

or

a complexing agent or complex having general formula X:



(X)

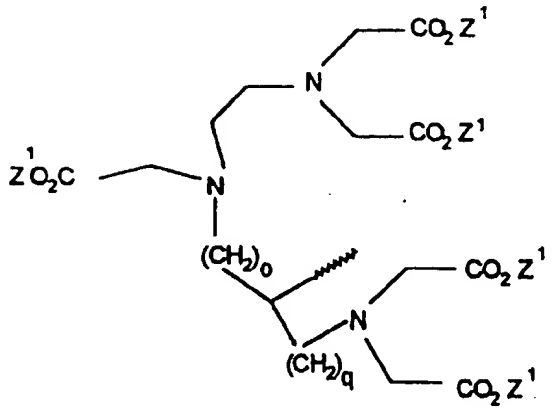
where R^3 and Z^1 have the above-mentioned meanings /141

or

or

a complexing agent or complex having general formula V:

/139

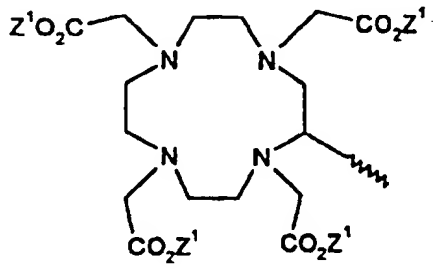


(V)

where Z^1 has the above-mentioned meaning and where o and q stand for the numbers 0 or 1 and yields the sum o + q = 1

or

a complexing agent or complex having general formula VI:

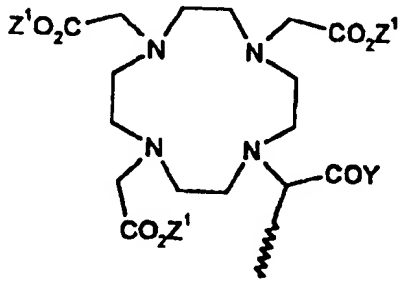


(VI)

where Z^1 has the above-mentioned meaning

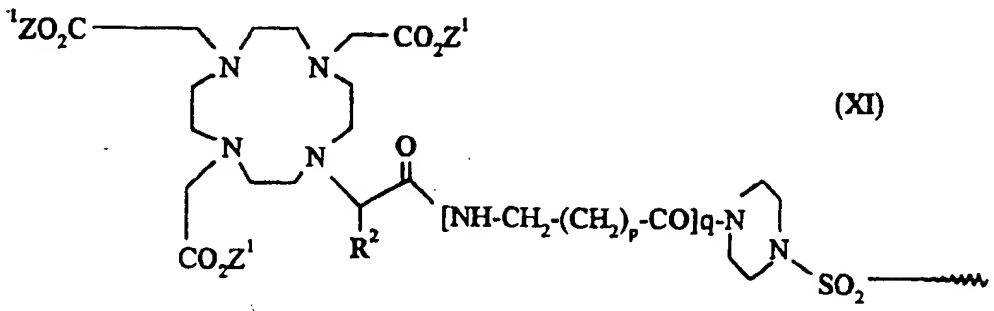
or

a complexing agent or complex having general formula VII:



(VII)

a complexing agent or complex having general formula XI:

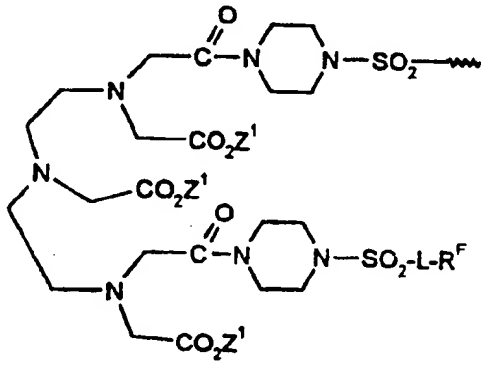


(XI)

where Z^1, p and q have the above-mentioned meaning and where R^2 has the meaning of R^1

or

a complexing agent or complex having general formula XII:



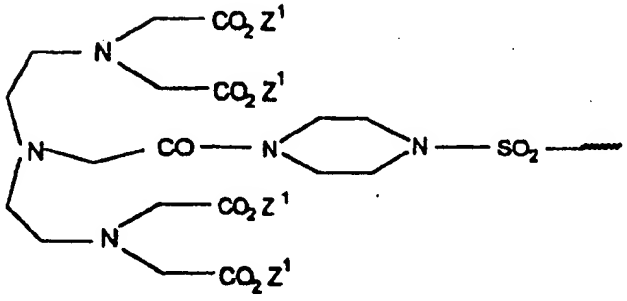
(XII)

where L, R^F and Z^1 have the above-mentioned meanings

or

a complexing agent or complex having general formula XIII:

/142



(XIII)

where Z^1 has the above-mentioned meaning.

2. Compounds according to Claim 1, characterized in that Z^1 represents a hydrogen atom.

3. Compounds according to Claim 1 or 2, characterized in that n in the formula $-C_nF_{2n}X$ represents the numbers 4-15.

4. Compounds according to one of Claims 1 to 3, characterized in that X in the formula $-C_nF_{2n}X$ represents a fluorine atom.

5. Compounds according to one of Claims 1 to 4, characterized in that L represents

$-CH_2-$
$-CH_2CH_2-$
$-(CH_2)_s-$ s = 3 - 15
$-CH_2-O-CH_2CH_2-$
$-CH_2-(O-CH_2-CH_2-)_t$ t = 2 - 6
$-CH_2-NH-CO-$
$-CH_2-NH-CO-CH_2-N(CH_2COOH)-SO_2-$
$-CH_2-NH-CO-CH_2-N(C_2H_5)-SO_2-$
$-CH_2-NH-CO-CH_2-N(C_{10}H_{21})-SO_2-$
$-CH_2-NH-CO-CH_2-N(C_6H_{13})-SO_2-$
$-CH_2-NH-CO-(CH_2)_{10}-N(C_2H_5)-SO_2-$

$-CH_2-NH-CO-CH_2-N(-CH_2-C_6H_5)-SO_2-$

$-CH_2-NH-CO-CH_2-N(-CH_2-CH_2-OH)SO_2-$

$-CH_2-NHCO-(CH_2)_{10}-S-CH_2CH_2-$

$-CH_2NHCOCH_2-O-CH_2CH_2-$

$-CH_2NHCO(CH_2)_{10}-O-CH_2CH_2-$

$-CH_2-C_6H_4-O-CH_2CH_2-$

$-CH_2-O-CH_2-C(CH_2-OCH_2CH_2-C_6F_{13})_2-CH_2-OCH_2-CH_2-$

$-CH_2-NHCOCH_2CH_2CON-CH_2CH_2NHCOCH_2N(C_2H_5)SO_2C_8F_{17}$

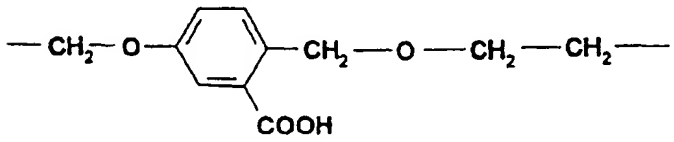
$CH_2-CH_2NHCOCH_2N(C_2H_5)-SO_2-$

$-CH_2-O-CH_2-CH(OC_{10}H_{21})-CH_2-O-CH_2CH_2-$

$-(CH_2NHCO)_4-CH_2O-CH_2CH_2-$

$-(CH_2NHCO)_3-CH_2O-CH_2CH_2-$

$-CH_2-OCH_2C(CH_2OH)_2-CH_2-O-CH_2CH_2-$



$-CH_2NHCOCH_2N(C_6H_5)-SO_2-$

$-NHCO-CH_2-CH_2-$

$-NHCO-CH_2-O-CH_2CH_2-$

$-NH-CO-$

$-NH-CO-CH_2-N(CH_2COOH)-SO_2-$

$-NH-CO-CH_2-N(C_2H_5)-SO_2-$

$-NH-CO-CH_2-N(C_{10}H_{21})-SO_2-$

$-NH-CO-CH_2-N(C_6H_{13})-SO_2-$

$-NH-CO-(CH_2)_{10}-N(C_2H_5)-SO_2-$

$-NH-CO-CH_2-N(-CH_2-C_6H_5)-SO_2-$

$-NH-CO-CH_2-N(-CH_2-CH_2-OH)SO_2-$

$-NH-CO-CH_2-$

$-CH_2-O-C_6H_4-O-CH_2-CH_2-$

$-CH_2-C_6H_4-O-CH_2-CH_2-$

$-N(C_2H_5)-SO_2-$

$-N(C_6H_5)-SO_2-$

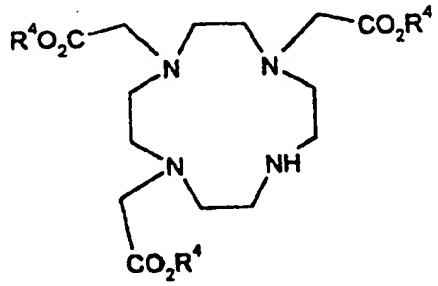
$-N(C_{10}H_{21})-SO_2-$

$-N(C_6H_{13})-SO_2-$

$-N(C_2H_4OH)-SO_2-$
$-N(CH_2COOH)-SO_2-$
$-N(CH_2C_6H_5)-SO_2-$
$-N-[CH(CH_2OH)_2]-SO_2-$
$-N-[CH(CH_2OH)CH(CH_2OH)]-SO_2-$
steht.

6. The compounds according to Claim 1:
Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-7-(perfluoroctylsulfonyl)-nonyl]-1,4,7,-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane,
Gadolinium complex of 10-[2-hydroxy-4-aza-5-oxo-7-aza-10,10,11,11,12,12,13,13,14,14,15,15,16,16,17,17,17-heptadecafluoro-heptadecyl]-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane.

7. Process for the production of perfluoroalkyl-containing compounds having general formula I, characterized in that
a) One makes compounds having general formula I with A having the meaning of general formula IX in that one mixes compounds having general formula 20:



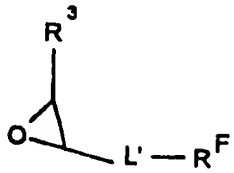
(20)

where

R^4 signifies hydrogen, methyl, ethyl, isopropyl, t-butyl or benzyl

with epoxide having general formula 21:

/145



(21)

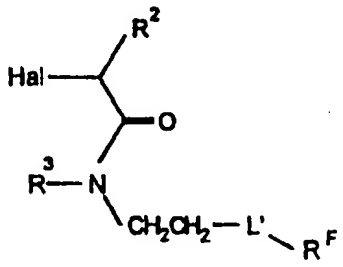
(21)

where

R^3 has the meaning of R^1, possibly in a protective form, or where it signifies $-(CH_2)_m-L-R^F$, where m can be 0, 1, or 2, where L' has the meaning of L, possibly in the protective form, and where R^F is a perfluorinated carbon chain,

in alcohols, ethers, water or in mixtures of water and an organic solvent at temperatures of between -10°C and 180°C, adding inorganic and/or organic bases after which one separates any possibly existing protective groups, where one mixes the resultant complexing agents with at least one metal oxide or metal salt of an element having the atomic numbers 21-29, 39, 42, 44 or 57-83 at room temperature or increased temperatures and where one then -- if desirable -- substitutes existing acidic hydrogen atoms with cations of inorganic and/or organic bases, amino acids or amino acid amides,

b) Compounds having general formula I with A having the meaning of general formula VIII are made in that one, in the known manner, alkylates compounds having general formula 20 with compounds having general formula 28:

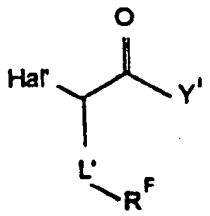


(28)

where R^2 has the meaning of R^1, where Hal signifies chlorine, bromine and iodine and where R^F, L' and R^3 have the above-mentioned meanings, /146

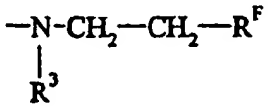
where one subsequently separates any possibly present protective groups and proceeds with the resultant complexing agents as indicated in a),

c) Compounds having general formula I with A having the meaning of general formula VII are made in that one, in the known manner, mixes compounds having general formula 20 with compounds having general formula 34:



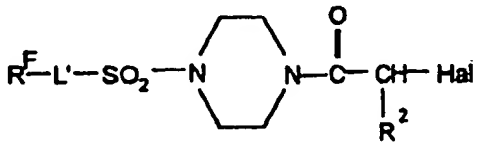
(34)

where Hal' has the meaning of Hal, F, -OTs, OMs, where Y' stands for the residues OH and



and where L' and R^F have the above-mentioned meanings, where one subsequently separates any possibly present protective groups and proceeds with the resultant complexing agents as indicated in a),

d) Compounds having general formula I with A having the meaning of general formula XI with q having the meaning of number 0 in that one mixes compounds having general formula 20 with compounds having general formula 68:

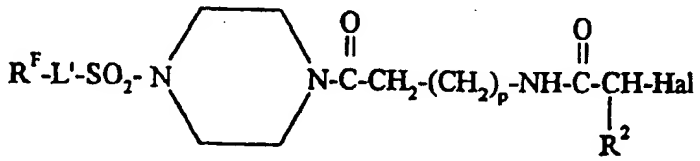


(68)

where R^F, L', R^2 and Hal have the above-mentioned meanings, /147

in an organic solvent at higher temperatures for several hours, where, thereafter, one separates any possibly present protective groups and proceeds with the resultant complexing agents as indicated in a),

e) Compounds having general formula I with A having the meaning of general formula XI with q having the meaning of number 1 in that one mixes compounds having general formula 20 with compounds having general formula 68a:



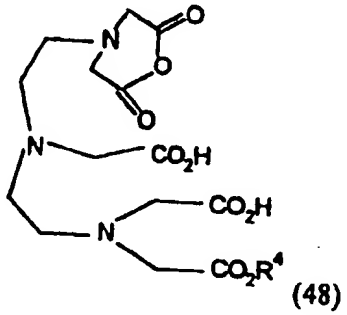
(68a) (68A)

where R^F, L', R^3, p and Hal have the above-mentioned meanings in an organic solvent at higher temperatures for

several hours, where, thereafter, one separates any possibly present protective groups and proceeds with the resultant complexing agents as indicated in a).

8. Process for the production of perfluoroalkyl-containing compounds having general formula 1, characterized in that

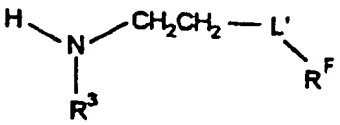
a) Compounds having general formula I with A having the meaning of general formula II in that, if Y in general formula II represents an OH group, one mixes compounds having general formula 48:



(48)

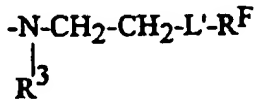
(48)

where R^4 has the above-mentioned meaning, /148

with an amine having general formula 29 

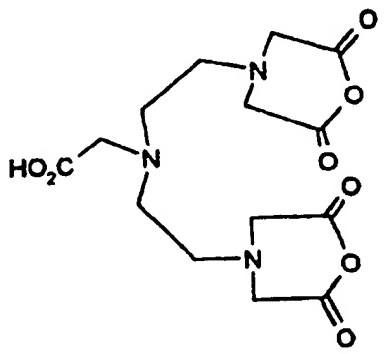
where R^3, L' and R^F have the above-mentioned meaning, in an inorganic solvent, possibly by adding inorganic and/or organic bases at higher temperatures, where one subsequently separates any possibly protective groups, where one mixes the resultant complexing agents with at least one metal oxide or metal salt of an element having atomic numbers 21-29, 39, 42, 44 or 57-83 at room temperature or at higher temperature and where one then -- if desired -- substitutes

any existing acidic hydrogen atoms with cations of inorganic and/or organic bases, amino acids or amino acid amides, or if Y in the general formula II represents a group:



(29)

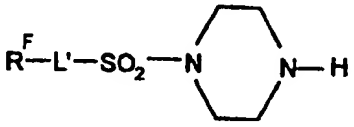
one mixes the bisanhydride of diethylene triamine-pentacetic acid (Merck) having general formula 49:



(49)

under similar conditions with an amine having formula 29 and proceeds further as in the first case,

b) Compounds having general formula I with A having the meaning of general formula XII in that one mixes the bisanhydride 49 with piperazine derivatives having general formula 67: -/149



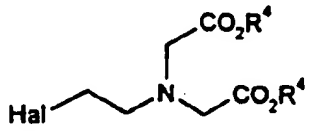
(67)

where R^F and L' have the above-mentioned meaning,

under the same conditions as given in a), where one subsequently separates any possibly present protective groups and where one continues to proceed as described in a).

9. Process for the production of perfluoroalkyl-containing compounds having general formula I, characterized in that

a) Compounds having general formula I with A having the meaning of general formula III in that one mixes the halogen carboxylic acid derivatives having general formula 52 in the known manner:

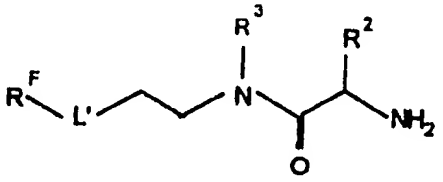


(52)

where Hal and R^4 have the above-mentioned meaning,

with compounds having general formula 51:

/150



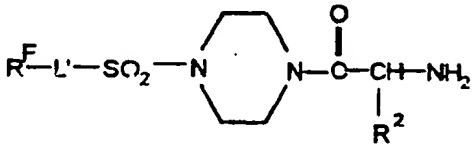
(51)

where R^F, L', R^2 and R^3 have the above-mentioned meaning,

where one subsequently separates any possibly present protective groups, where one mixes the resultant complexing agents with at least one metal oxide or metal salt of an element having atomic numbers 21-29, 39, 42, 44 or 57-83 at

room temperature or increased temperature and where one then -- if desired -- substitutes any existing acidic hydrogen atoms with cations of inorganic and/or organic bases, amino acids or amino acid amides,

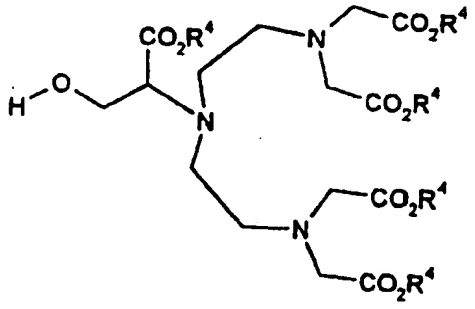
b) Compounds having general formula I with A having the meaning of general formula XIII in that, in analogy to a), one mixes the halogen carboxylic acid derivatives having general formula 52 with piperazine derivatives having general formula 66:



(66)

where R^F, L' and R^2 have the above-mentioned meaning, and where one subsequently separates any possibly present protective groups and where one continues to proceed as described in a).

10. Process for the production of perfluoroalkyl-containing compounds having general formula I, characterized in that one makes compounds with A having the meaning of general formula IV in that one mixes hydroxy acids or hydroxy esters having general formula 56:



/151

(56)

where R^4 has the above-mentioned meaning,

with halogen compounds having general formula 55:

(55)

$$Hal\text{-}L'\text{-}R^F$$

where R^F, L', and Hal have the above-mentioned meanings,

in a mixture consisting of an organic solvent and a buffer at a slightly alkaline pH at room temperature over several hours, where one subsequently separates any possibly protective groups, where one mixes the resultant complexing agents with at least one metal oxide or metal salt of an element having atomic numbers 21-29, 39, 42, 44 or 57-83 at room temperature or increased temperature and where one then -- if desired -- substitutes any existing acidic hydrogen atoms with cations of inorganic and/or organic bases, amino acids or amino acid amides.

11. Process for the production of perfluoroalkyl-containing compounds having general formula I, characterized in that

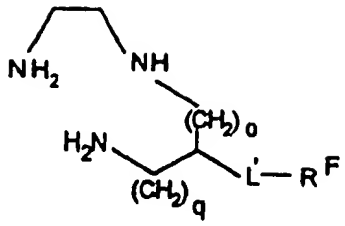
a) Compounds having general formula I with A having the meaning of general formula V in that one mixes a-halogen carboxylic acid esters or acids having general formula 18: /152

(18)

$$Hal\text{-}CH_2CO_2R^4$$

where Hal and R^4 have the above-mentioned meaning,

with amines having general formula 39:

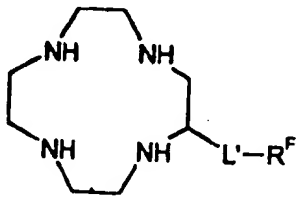


(39)

where L', R^F, o and q have the above-mentioned meanings,

where one subsequently separates any possibly present protective groups, where one mixes the resultant complexing agents with at least one metal oxide or metal salt of an element having atomic numbers 21-29, 39, 42, 44 or 57-83 at room temperature or increased temperature and where one then -- if desired -- substitutes any existing acidic hydrogen atoms with cations of inorganic and/or organic bases, amino acids or amino acid amides,

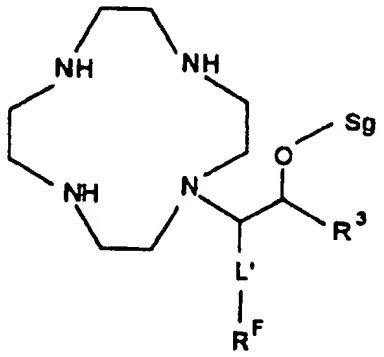
b) Compounds having general formula I with A having the meaning of general formula VI in that one mixes in the known manner a-halogen carboxylic esters or acids having general formula 18 with compounds having general formula 36:



(36)

where L' and R^F have the above-mentioned meanings, /153 and where one proceeds further as described in a).

c) Compounds having general formula I with A having the meaning of general formula X in that one mixes in the known manner a-halogen carboxylic esters or acids having general formula 18 with compounds having general formula 70:



(70)

where R^F, L', R^3 have the above-mentioned meanings and where Sg has the meaning of a protective group,

and where one further proceeds as described in a).

12. Pharmaceutical substances containing at least one physiologically tolerable compound according to Claim 1, possibly with the additives customary in galenics.

13. Use of at least one physiologically tolerable compound according to Claim 1 or a pharmaceutical substance according to Claim 10 as contrast medium in ^{1}H-NMR diagnosis and spectroscopy.

14. Use of at least one physiologically tolerable compound according to Claim 1 or a pharmaceutical substance according to Claim 10 as contrast medium in x-ray diagnostics.

15. Use of at least one physiologically tolerable compound according to Claim 1 or a pharmaceutical substance according

to Claim 10 as pharmaceutical agent for radiodiagnosis and radiotherapy.

16. Use according to Claim 13 or 14 as blood pool agents.

17. Use according to Claim 13 or 14 as lymphographics.

Diagram 1. /1/2

[Key: 1) % of injected dose; 2) Example 1].

Figure 1. MRT Lymph Node Presentation After Interstitial Administration of Contrast Medium /2/2

[Key: 1) MR imaging before and after interstitial application of 10 μmol Gd/kg Gd-DO3A-γ-amino amide-perfluoroctyl ether; 2) Precontrast; 3) 120 minutes p.i.].3) T1-weighted spin-echo sequence (TR 400/TE 15); Guinea pigs, injection site: interdigital space, hind paw (unilaterally); Arrows: popliteal and inguinal profound lymph node on injection side].

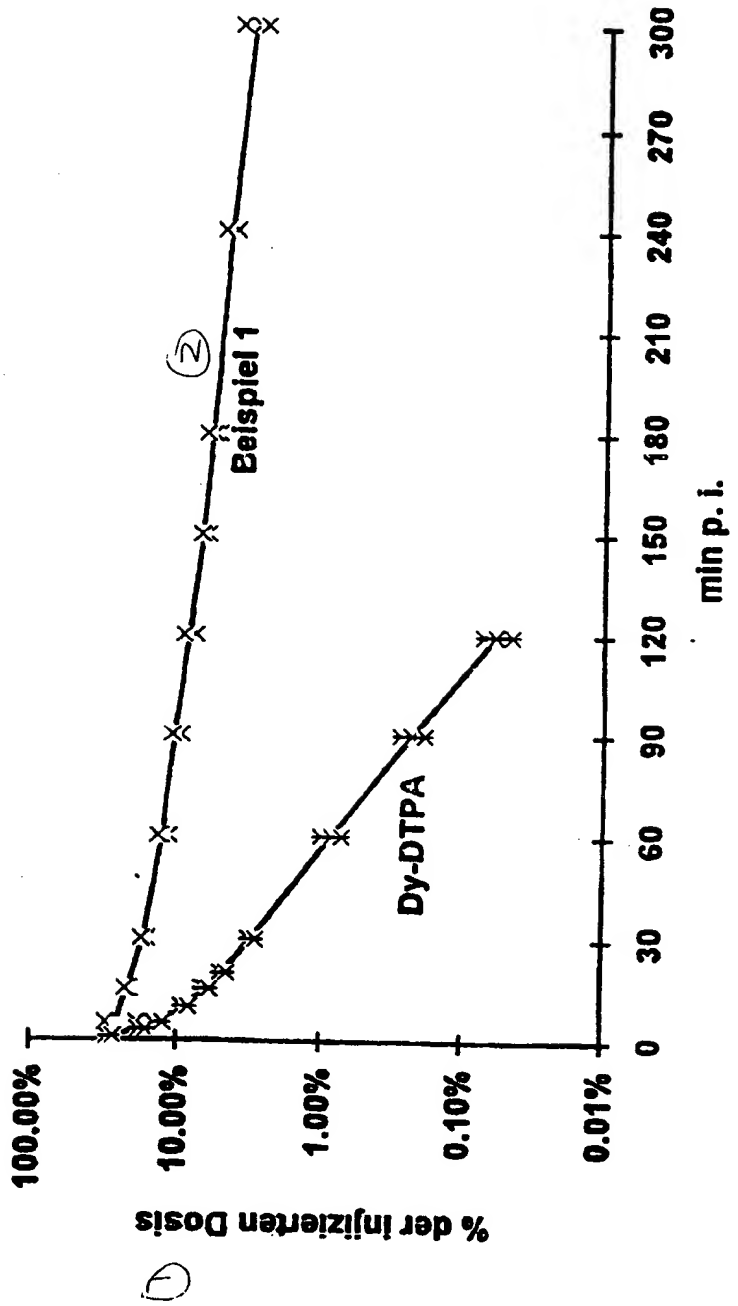

Beispiel 1
Dy-DTPA
100.00%
10.00%
1.00%
0.10%
0.01%
% der injizierten Dosis
0
30
60
90
120
150
180
210
240
270
300
min p. i.

Abbildung 1

Bild 1: MRT-Lymphkonotendarstellung nach interstitieller Gabe des Kontrastmittels